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(54) Title: 32 HUMAN SECRETED PROTEINS

(57) Abstract: The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating diseases, disorders, and/or conditions related to these novel human secreted proteins.



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32 Human Secreted Proteins

Field of the Invention

This invention relates to newly identified polynucleotides, polypeptides encoded by these polynucleotides, antibodies that bind these polypeptides, uses of
5 such polynucleotides, polypeptides, and antibodies, and their production.

Background of the Invention

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or
10 organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic
15 reticulum (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

20 Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in
25 secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins
30 include the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of

the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical diseases, disorders, and/or conditions by using secreted proteins or the genes that encode them.

Summary of the Invention

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant and synthetic methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting diseases, disorders, and/or conditions related to the polypeptides and polynucleotides, and therapeutic methods for treating such diseases, disorders, and/or conditions. The invention further relates to screening methods for identifying binding partners of the polypeptides.

Detailed Description

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5 kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the

ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

5 A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC
10 (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions.
15 Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl;
20 0.2M NaH₂PO₄; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the
25 inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above,
30 due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA⁺ sequences (such as any 3' terminal polyA⁺ tract of a cDNA shown in the sequence listing), or to a

complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

5 The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of
10 single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA
15 backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

 The polypeptide of the present invention can be composed of amino acids
20 joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more
25 detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of
30 modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or

may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

"SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

Many proteins (and translated DNA sequences) contain regions where the amino acid composition is highly biased toward a small subset of the available residues. For example, membrane spanning domains and signal peptides (which are also membrane spanning) typically contain long stretches where Leucine (L), Valine

(V), Alanine (A), and Isoleucine (I) predominate. Poly-Adenosine tracts (polyA) at the end of cDNAs appear in forward translations as poly-Lysine (poly-K) and poly-Phenylalanine (poly-F) when the reverse complement is translated. These regions are often referred to as "low complexity" regions.

5 Such regions can cause database similarity search programs such as BLAST to find high-scoring sequence matches that do not imply true homology. The problem is exacerbated by the fact that most weight matrices (used to score the alignments generated by BLAST) give a match between any of a group of hydrophobic amino acids (L, V and I) that are commonly found in certain low complexity regions almost
10 as high a score as for exact matches.

 In order to compensate for this, BLASTX.2 (version 2.0a5MP-WashU) employs two filters ("seg" and "xnu") which "mask" the low complexity regions in a particular sequence. These filters parse the sequence for such regions, and create a new sequence in which the amino acids in the low complexity region have been
15 replaced with the character "X". This is then used as the input sequence (sometimes referred to herein as "Query" and/or "Q") to the BLASTX program. While this regime helps to ensure that high-scoring matches represent true homology, there is a negative consequence in that the BLASTX program uses the query sequence that has been masked by the filters to draw alignments.

20 Thus, a stretch of "X"s in an alignment shown in the following application does not necessarily indicate that either the underlying DNA sequence or the translated protein sequence is unknown or uncertain. Nor is the presence of such stretches meant to indicate that the sequence is identical or not identical to the sequence disclosed in the alignment of the present invention. Such stretches may
25 simply indicate that the BLASTX program masked amino acids in that region due to the detection of a low complexity region, as defined above. In all cases, the reference sequence(s) (sometimes referred to herein as "Subject", "Sbjct", and/or "S") indicated in the specification, sequence table (Table 1), and/or the deposited clone is (are) the definitive embodiment(s) of the present invention, and should not be construed as
30 limiting the present invention to the partial sequence shown in an alignment, unless specifically noted otherwise herein.

Polynucleotides and Polypeptides of the Invention

FEATURES OF PROTEIN ENCODED BY GENE NO: 1

The translation product of this gene shares sequence homology with
 5 alloreaction associated antigen (ARAg), or V7, a transmembrane protein with an
 extracellular domain containing 7 immunoglobulin like domains. ARAg is present on
 the surface of alloantigen activated CD8+ T cells, monocytes, granulocytes and
 peripheral dendritic cells and can be used to screen potential immunosuppressants,
 identify and isolate ARAg receptors and generate MAb for suppressing an immune
 10 response. A mAb directed against V7 inhibits the proliferative response of T cells to
 allogenic cells or immobilized anti-CD3 Ab, but not lectin mitogens, suggesting that
 V7 plays a role in TCR/CD3-mediated T cell activation. Based on the sequence
 similarity, the translation product of this clone is expected to share at least some
 biological activities with T-cell activator proteins, and particularly V7. Such activities
 15 are known in the art, some of which are described elsewhere herein (See, for example,
 J. Immunol. 154 (9), 4434-4443 (1995); all the information available through this
 reference is hereby incorporated herein by reference).

A preferred polypeptide variant of the invention comprises the following
 amino acid sequence:

20 MGALRPTLLPPSLPLLLLLMLGMGCWAREVLVPEGPLYRVAGTAVSISCNVT
 GYEGPAQQNFEWFLYRPEAPDTALGIVSTKDTQFSYAVFKSRVVAGEVQVQR
 LQGDVAVLKIARLQAQDAGIYECHTPSTDTRYLGSYSGKVELRVLPDVLQVS
 AAPPGPRGRQAPTSPPRMTVHEGQELALGCLARTSTQKHTHLAVSFGRSVPE
 APVGRSTLQEVVGIRSDLAVEAGAPYAERLAAGELRLGKEGTDYRMMVV
 25 GGAQAGDAGTYHCTAAEWIQDPDGSWAQIA (SEQ ID NO: 153). Moreover,
 fragments and variants of these polypeptides (such as, for example, fragments as
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
 which hybridizes, under stringent conditions, to the polynucleotide encoding these
 30 polypeptides, or the complement thereof are encompassed by the invention.
 Antibodies that bind polypeptides of the invention are also encompassed by the

invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 580 - 596 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 597 to 648 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

This gene is expressed primarily in brain and primary dendritic cells and to a lesser extent in activated T cells, as well as several other tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to: neurodegenerative disorders; immune system dysfunction; immunosuppression; transplant rejection; graft versus host disease; inflammatory disorders; and autoimmune diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, CNS, and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes shown in SEQ ID NO: 82 as residues: Thr-52 to Phe-62, Pro-130 to Arg-135, Pro-160 to Arg-173, Thr-190 to His-195, Gly-246 to Arg-252, Arg-397 to Thr-403, Gly-414 to Arg-420, Arg-483 to Glu-488, Arg-525 to Arg-530, Gly-535 to Val-541. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution in primary dendritic cells and activated T cells, combined with the homology to ARAg or V7 indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of a variety of immune disorders. Previous studies have indicated that V7 or ARAg is involved in T cell activation and in immune responses. Therefore, this gene may play similar roles, and may be involved in inflammation, autoimmunity, susceptibility to infection, tissue/graft rejection, and in the proliferation, survival, differentiation, or activation of a variety of hematopoietic cell lineages. Similarly, expression at elevated levels in the brain, and in other tissues, suggests that this protein may be involved in the proliferation, stimulation, or differentiation of other cell lineages as well, including neurons and mesenchymal cells. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological

activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence
10 would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2315 of SEQ ID NO:11, b is an integer of 15 to 2329, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a
15 + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 2

The translation product of this gene shares sequence homology with the PC-1 protein, that is a membrane glycoprotein that is selectively expressed on the surface of
20 antibody-secreting cells. It also displays homology with alkaline phosphodiesterase I, and autotaxin, a tumor cell motility-stimulating protein. Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with membrane glycoprotein and/or autotaxin proteins. Such activities are known in the art, some of which are described elsewhere herein.

25 The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 411 - 427 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 428 to 453 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia
30 membrane proteins.

This gene is expressed primarily in human ovarian tumors.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to: reproductive diseases and/or disorders, particularly ovarian cancer and tumor cell metastasis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, ovarian, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 83 as residues: Gly-17 to His-22, Lys-100 to Asp-109, Gln-124 to Ser-130, Glu-186 to Glu-201, Asp-237 to Lys-247, His-304 to Ile-311, Asp-335 to Leu-342, Ala-355 to Thr-364, Pro-382 to His-391, Gln-444 to Leu-451. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution in ovarian cancer and homology to autotaxin indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of cancer. Autotaxin is a tumor cell motility-stimulating protein. The gene described herein in this patent application is only detected in ovarian tumors. Therefore, it may represent a key player in the diagnosis or treatment in particular of ovarian cancer, and possibly of cancers in general. It may particularly represent a target for inhibitors to control the spread of such cancers. Similarly, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and

elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in

5 acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Alternatively, this gene product may be involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers.

10 Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types

15 of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new

20 insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or

25 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

30 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 2316 of SEQ ID NO:12, b is an integer of 15 to 2330, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 3

The translation product of this gene shares sequence homology with murine proline-rich acidic protein (Genbank Accession No: AAC24897).

This gene is expressed primarily in fetal liver and tumors of the liver (hepatoma) and to a lesser extent in normal and malignant colon as well as breast cancer.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to:

15 inflammatory diseases and/or cancers of the liver, colon or breast. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal or hepatic system, expression of this gene at significantly higher or lower levels may

20 be routinely detected in certain tissues or cell types (e.g., gastrointestinal, hepatic, metabolic, reproductive, endocrine, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, breast milk, chyme, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in

25 healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes shown in SEQ ID NO: 84 as residues: Trp-35 to Trp-46, Pro-53 to Asp-58, Thr-74 to Arg-83, Pro-106 to Leu-113, Pro-116 to Arg-128, Pro-141 to Gln-152. Polynucleotides encoding

30 said polypeptides are also encompassed by the invention.

The tissue distribution in human colon tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and or treatment

of tumors of the colon or liver or for inflammatory disorders of these tissues such as inflammatory bowel disease. Moreover, the protein product of this clone is useful for the detection and treatment of liver disorders and cancers. Representative uses are described in the "Hyperproliferative Disorders", "Infectious Disease", and "Binding Activity" sections below, in Example 11, and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells. In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. The protein is useful for modulating the immune response to aberrant polypeptides, as may exist in rapidly proliferating cells and tissues (e.g., colon, breast, and liver cancer tissue). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 637 of SEQ ID NO:13, b is an integer of 15 to 651, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

30 FEATURES OF PROTEIN ENCODED BY GENE NO: 4

The translation product of this gene shares sequence homology with the human complement subcomponent C1q chain A precursor (see, e.g., GenBank accession AAD32626), which is thought to be important in immune responses.

It has been discovered that this gene is expressed primarily in immune and
5 haemopoietic cells and to a lesser extent in various cancer cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: disorders of the immune and haemopoietic systems and cancer. Similarly, polypeptides and antibodies directed to
10 those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and haemopoietic systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine,
15 synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ
20 ID NO: 85 as residues: Pro-29 to Gly-46, Lys-48 to Gly-55, Lys-67 to Gly-80, Lys-100 to Pro-115, Arg-121 to Gly-127, Asn-139 to Gly-149, Ser-179 to Arg-185, Asp-191 to Gly-196, Lys-219 to Gly-224. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution and homology to complement subcomponent C1q chain
25 A precursor suggests that the protein product of this clone would be useful for treatment and diagnosis of diseases of the immune and haemopoietic systems and cancers. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the
30 proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness

in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, 5 rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus 10 erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma.

Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem 15 cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Based upon the tissue distribution of this protein, antagonists directed against this protein may be useful in blocking the activity of this protein. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene. Also provided is a kit for detecting tumors in 20 which expression of this protein occurs. Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody 25 binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to 30 identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 983 of SEQ ID NO:14, b is an integer of 15 to 997, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 5

The translation product of this gene shares sequence homology with, and is believed to be a novel homolog of, the human complement C1r protein (gb|AAA51851.1| human complement C1r [Homo sapiens]) an inactive precursor of a serine protease which is thought to be important in activation of the complement pathway in human immunity (See, for example, Biochemistry 25 (17), 4855-4863 (1986); all information within this reference is hereby incorporated herein by reference). The homologous regions are shown below:

```

>gb|AAA51851.1| human complement C1r [Homo sapiens] >pir|A24170|C1HURB
complement subcomponent C1r (EC 3.4.21.41) precursor - human
>sp|P00736|C1R_HUMAN COMPLEMENT C1R COMPONENT PRECURSOR (EC
3.4.21.41).
Length = 705

Plus Strand HSPs:

Score = 721 (253.8 bits), Expect = 7.4e-103, Sum P(2) = 7.4e-103
Identities = 127/230 (55%), Positives = 170/230 (73%), Frame = +1

Query:  574 AKVQNHCEPYYQXXXXXXXXXX-----XXXKWKDRQDGEEVLQCMFVCGRPVTPIA 729
      A++Q +C EPYY+                               WK+ Q GE++ +C+PVCG+PV P+
Sbjct:  400 ARIQYYCHEPYYKMQTRAGSRESEQGVYTCTAAGIWKNEQKGEKIPRCLPVCCKPVPNPVE 459

Query:  730 QNQTTLGSSRAKLGNFPPWQAFSTIHGRGGGALLGDRWILTAAHTIYPKDSVSLRKNQSVN 909
      Q Q  +G  +AK+GNFPWQ FT+IHGRGGGALLGDRWILTAAHT+YPK+  + + N S++
Sbjct:  460 QRQRIIGGQKAKMGNFPPWQVFTNIHGRGGGALLGDRWILTAAHTLYPKEHEA-QSNASLD 518

Query:  910 VFLGHTAIDEMKLGNHNPVHRVVHPDYRQNESHNFSGDIALLELQHSIPLGPNVLPVCL 1089
      VFLGHT ++E++KLGNNP+ RV VHPDYRQ+ES+NF GDIALLEL++S+ LGPN+LP+CL
Sbjct:  519 VFLGHTNVEELMKLGNNHPIRRVSVHPDYRQDESYNFEKDIALLELENSVTLPNLLPICL 578

Query:  1090 PDNETLYRSGLLGYVSGFGMEMGWLTTTELKYSRLPVAPREACNAWLQKRQR 1242
      PDN+T Y  GL+GYVSGFG+  + +L++ RLPVA  +AC WL+ + R
Sbjct:  579 PDNDTFYDLGLMGYVSGFGVMEEKIAHDLRFVRLPVANPQACENWLRGKNR 629

Score = 325 (114.4 bits), Expect = 7.4e-103, Sum P(2) = 7.4e-103

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Identities = 72/156 (46%), Positives = 94/156 (60%), Frame = +1

5 Query: 79 MWLLLLWGVQLQACPTRGSGVLLAQELPQQLTSPGYPEPYGKGQESSTDIKAPEGFAVRLVF 258
 MW L L C GS+ + Q+L ++TSP +P+PY E++T I P G+ V+LVF
 Sbjct: 1 MWLLYLLVPALFCRAGGSIPIPKLFGEVTSPLFPKPYPNNFETTTVITVPTGYRVKLVF 60

10 Query: 259 QDFDLEPSQDCAGDSVTISFVGSDPSQFCGQGSPLGRPPGQREFVSSGRSLRLTFRTQP 438
 Q FDLEPS+ C D V IS +FCGQ GSPLG PPG++EF+S G + LTF T
 Sbjct: 61 QQFDLEPSEGCFYDYVKISADKSLGRFCGQLGSPNGPKKEFMSQGNKMLLTFHTDF 120

Query: 439 SSE-NKTAHLHKGFLALYQTVAVNYSQPISEASRGSE 546
 S+E N T +KGFLA YQ AV+ + S + G E
 Sbjct: 121 SNEENGTIMFYKGFLLAYYQ--AVDLDECASRSKSGEE 155

- 15 Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with serine protease zymogens such as C1r. Such activities are known in the art, some of which are described elsewhere herein.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of the following amino acid sequence:

- 20 MGLILTVVGVHNDTVDRVVPQFQHLYGCVAQEHIHTLVLPERNTVLGVDGV
 GSS
 EDPSVPQQGPAPTAVDTGEGLPGEVAQLGSGRTEGRLILGNGGDWPSADRHT
 LKNLLPILSVFPGPWGCTGECPCCRGLIIGLLAVVLDLGRVVSRCVDGLRAPA
 GLADGLTIVHSHGLVEGQEALVEVGSLVLRGRLCA EGQPQTPP (SEQ ID NO:
 25 154). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
 30 encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

- This gene is expressed primarily in kidney (e.g., fetal kidney, rejected Kidney
 35 transplant, and cancerous kidney tissue) Human OB MG63 control fraction I (osteosarcoma); Human Adult Testes, Large Inserts, Reexcision; and Rejected Kidney, lib 4.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include but are not limited to: reproductive, and renal diseases and/or disorders, including immune suppression and other diseases of the immune system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential
5 identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune,, renal, reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, seminal fluid, plasma, urine, synovial fluid and
10 spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ
15 ID NO: 86 as residues: Pro-32 to Lys-49, Glu-66 to Ala-72, Asp-84 to Gly-90, Arg-117 to Thr-126, Pro-161 to Tyr-176, Gly-191 to Glu-201, Leu-270 to Ser-275, Pro-303 to Ser-314, Asp-339 to Tyr-344, Gln-384 to Lys-396. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The homology of the translation product of this gene to the human C1r
20 indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of diseases of the immune system including AIDS and other immune deficiencies, autoimmune disorders such as lupus, and other immune disorders. Alternatively, the distribution in testicular tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for the
25 treatment and diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, this gene product is useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) are useful as male contraceptive agents. Similarly, the protein is believed to be useful
30 in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that is expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other

specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Alternatively, the tissue distribution in kidney indicates that the protein product of this clone could be used in the treatment and/or

5 detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. The protein is useful in

10 modulating the immune response to aberrant polypeptides (as may exist in rapidly proliferating cells and tissues), and presents a novel therapeutic for hemophiliacs and other patients presenting aberrant blood diseases and/or disorders. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their

15 interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

20 related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

25 general formula of a-b, where a is any integer between 1 to 1252 of SEQ ID NO:15, b is an integer of 15 to 1266, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

30 **FEATURES OF PROTEIN ENCODED BY GENE NO: 6**

The translation product of this gene shares sequence homology with *Bos taurus* mimecan (see GenBank accession AAB70264), which is thought to be

important in connective tissues. Based on this homology it is expected that these proteins will share some biological activity.

It has been discovered that this gene is expressed primarily in fetal tissues, aorta, cochlea and to a lesser extent in a variety of other tissues and cell types.

5 Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound healing, deafness and vertigo. Similarly, polypeptides and antibodies directed to those polypeptides are useful to
10 provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the connective tissue, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., immune, nervous, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from
15 an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 87 as residues: Pro-21 to Arg-28, Tyr-33 to Phe-38, Gln-45 to Glu-61, Pro-83
20 to Glu-90, Lys-195 to Ile-204, Thr-253 to Tyr-262. Polynucleotides encoding said polypeptides are also encompassed by the invention.

Mimecan is a member of a group of small, leucine-rich proteoglycans (SLRPs). These proteins share a common core structure which consists of a central domain with varying numbers of leucine-rich repeats flanked by cysteine-rich
25 clusters. Seven members of SLRPs have been described so far. These include: keratocan, lumican, fibromodulin, decorin, biglycan, and epiphykan. A seventh member of the family, mimecan, is a proteoglycan expressed by many connective tissues. It was originally isolated in a truncated form as a bone-associated glycoprotein, osteoglycin. Mimecan has since been demonstrated to be expressed in a
30 variety of tissues, with and without keratan sulfate chains. Numerous examples illustrate the ability of SLRPs to bind growth factors and/or growth factor receptors and therefore to modulate cell proliferation and differentiation.

The tissue distribution and homology to mimecan suggests that the protein product of this clone would be useful for the treatment and diagnosis of conditions involving tissue repair and wound healing. Tissue repair may be indicated in cases of injury to the skin or internal organs, ulceration, cellular necrosis or other conditions involving healing of both diseased or non-diseased, traumatized tissue.

More specifically, the expression in aorta would suggest a role in cardiovascular disorders such as, asthma, heart disease, restenosis, atherosclerosis, stroke, angina and thrombosis. The expression in cochlea would suggest a potential use in the treatment of conditions affecting the inner ear, such as deafness and vertigo.

Based upon the tissue distribution of this protein, antagonists directed against this protein may be useful in blocking the activity of this protein. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene. Also provided is a kit for detecting tumors in which expression of this protein occurs. Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein. In addition, because of the implications of tissue regeneration, remodeling and growth regulation, and in light of the high degree of expression in fetal and cancerous tissues, the protein product of this gene may have indications in the diagnosis and treatment of neoplasms and cancer. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the
5 general formula of a-b, where a is any integer between 1 to 2696 of SEQ ID NO:16, b is an integer of 15 to 2710, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

10 **FEATURES OF PROTEIN ENCODED BY GENE NO: 7**

The translation product of this gene shares sequence homology with the rat decay accelerating factor (see, e.g., GenBank accession AAC77439) which is thought to be important in modifying the activity and cellular response of complement proteins and thus attenuating complement mediated immune responses.

15 It has been discovered that this gene is expressed primarily in ovarian tumor.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: reproductive diseases and/or disorders, particularly ovarian tumors. Similarly, polypeptides and antibodies directed
20 to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., reproductive, ovarian, and cancerous and wounded tissues) or bodily fluids (e.g.,
25 lymph, amniotic fluid, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

The tissue distribution in ovarian tumor tissue indicates that polynucleotides and polypeptides of the invention are useful for the detection, treatment, and/or
30 prevention of proliferative diseases and/or disorders, and particularly for ovarian cancer. Moreover, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may

show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions
5 involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Alternatively, this gene product
10 may be involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue
15 regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection,
20 treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation.

Based upon the tissue distribution of this protein, antagonists directed against
25 this protein may be useful in blocking the activity of this protein. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene. Also provided is a kit for detecting tumors in which expression of this protein occurs. Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of
30 detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen

found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein. Furthermore, the protein may also be used to determine biological activity, to raise
5 antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly
10 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention
15 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2391 of SEQ ID NO:17, b is an integer of 15 to 2405, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

20 FEATURES OF PROTEIN ENCODED BY GENE NO: 8

Angiogenesis, the formation of new blood vessels from pre-existing vasculature, is a tightly regulated process in normal adults. Under physiological circumstances, growth of new capillaries is tightly controlled by an interplay of
25 growth regulatory proteins which act either to stimulate or to inhibit blood vessel growth. Normally, the balance between these forces is tipped in favor of inhibition and consequently blood vessel growth is restrained. Under certain pathological circumstances, however, local inhibitory controls are unable to restrain the increased activity of angiogenic inducers. Angiogenesis is a key step in the metastasis of cancer
30 (Folkman, *Nature Med.* 1:27-31 (1995)) and in abnormal wound healing, inflammation, rheumatoid arthritis, psoriasis, and diabetic retinopathy, it is integral to the pathology (Folkman *et al.*, *Science* 235:442-447 (1987)), engendering the hope

that these pathological entities could be regulated by pharmacological and/or genetic suppression of blood vessel growth (Iruela-Arispe *et al.*, *Thromb. Haem.* 78:672-677 1997)).

Thrombospondin-1 (TSP-1) is a 450 kDa, anti-angiogenic adhesive glycoprotein released from activated platelets and secreted by growing cells (reviewed in Adams, *Int. J. Biochem. Cell. Biol.* 29:861-865 (1997)). TSP-1 is a homotrimer, with each subunit comprised of a 1152 amino acid residue polypeptide, post-translationally modified by *N*-linked glycosylation and beta-hydroxylation of asparagine residues.

TSP-1 protein and mRNA levels are regulated by a variety of factors. TSP-1 protein levels are downregulated by IL-1 alpha and TNF alpha. TSP-1 mRNA and protein levels are upregulated by polypeptide growth factors including PDGF, TGF-beta, and bFGF (Bornstein, *Faseb J.* 6: 3290-3299 (1992)) and are also regulated by the level of expression of the p53 tumor suppressor gene product (Dameron *et al.*, *Science* 265:1582-1584 (1994)). At least four other members of the thrombospondin family have been identified: TSP-2, TSP-3, TSP-4, and TSP-5 (also called COMP). There is a need in the art to identify other molecules involved in the regulation of angiogenesis.

Figure 4A-4H shows the nucleotide sequence (SEQ ID NO:18) and the deduced amino acid sequence (SEQ ID NO:89) of THRAP. The predicted leader sequence located at about amino acid residues 1 to 28 is bolded in Figure 4A-4H. Figure 4A-4H also shows 13 TSP-1-like domains (indicated by single underlined amino acid residues), an IgG-like domain (indicated by bolded and double underlined amino acid residues), and a proteinase inhibitor-like domain (indicated by double underlined amino acid residues) of SEQ ID NO: 89. In this context "about" includes the particularly recited ranges, larger or smaller by several (10, 9, 8, 7, 6, 5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Figure 5A-5E shows the regions of identity between the amino acid sequence of THRAP and the translation product of Thrombospondin-like protein

MKCSYTVVFLFYLLIASFHVDALSWAAWSPWSSCTKTCGGGVSRQLRRCLT
SKCSGESVRFKVCAQKTCESKSRLARDTICGGEIIVSRGQCEVVCRSRLTGAN
FLWRVDDGTPCQAATSRVCSKGSCQIVGCDGLISSFRFDACGVCGGRGDT

CDNGKFIWKVSEEYTACASNCDIDVDWSGAGRSIASTSQPIVVCVNAITGRVV
 PEKLCADKLRPKVEARPCPMLICPSRWMAADWTECVPHCGEGTRKREYVCV
 QTAHNVTVHVPDTCENGTRPAAEENCVSTSCGRWEAGKWSKCTASCGQGV
 RRRHVACVGGSDCDEGGRPRQETTCYAGIPCSIATNSLDWNDRAYLDGNTFG
 5 SMDNHNDWQAPRLVAGEWSTCSSTCGTGVMSTVECVAVNPISAPIKLPMSE
 ECQDQEQPKLFESCEVRSCPLQEDSKLSEDEAPYQWRYGDWTQCSASCLGGK
 QKAALKCIQVSTGKSVQWSQCDARRRPPEKSRPCNQHPCPFWLTSKYSDCS
 MSCGSGTARRSVKCAQTVSKTDGADAHIVLRDDRCHFKKPQETETCNVVAC
 PATWVSSLNKRHNKIKLNKLKTAQWTECSRSCDSGERRRQVWCEIRDSRGKT
 10 QRRPDVECDANTKPQTVEVCSFGSCSRPELLSNRVFEQNAEQKKLTLGIGGVA
 TLYQGTSIKIKCPAKKFDKKKIYWKKNGKKIKNDAHIKVSANGNLRVHFARM
 EDAGVYECFTDRLQGNVTLNFKYRDFPASRVDLAPKPQIPSTKNRQRVQVSK
 EDVLREQASVLHKMNVSLIEALLTAPNDEKAREQLRKYGNELVARWDIGHW
 SECRQKTCHVAGYQARGISCKVTFHGEIRNVDNSICESLASVRPPETRPCHRE
 15 DCPRWEASQWSECSSQRCVSSMLAQKRRNVTCRFTNGTSVDIQHCDITNRPA
 TTMDCPNQNCXAEWRTSDWGSSESCEGTGGVQLRLLSCVWISSGRPAGRNC
 EQMRRPHSARACVADEPLPPCMPTASALYQRDASCQDQSRFCDIKLFHSCDS
 LEVRQKCCSTCTFVERKKF (Genbank accession CAB03121.1) determined by
 BLAST analysis. Identical amino acids between the two polypeptides are boxed. By
 20 examining the regions of boxed amino acids, the skilled artisan can readily identify
 conserved domains between the two polypeptides. These conserved domains are
 preferred embodiments of the present invention.

Figure 6 shows an analysis of the THRAP amino acid sequence. Alpha, beta,
 turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions;
 25 flexible regions; antigenic index and surface probability are shown, and all were
 generated using the default settings. In the "Antigenic Index or Jameson-Wolf" graph,
 the positive peaks indicate locations of the highly antigenic regions of the THRAP
 protein, i.e., regions from which epitope-bearing peptides of the invention can be
 obtained. The domains defined by these graphs are contemplated by the present
 30 invention.

The data presented in Figure 6 are also represented in tabular form in Table 7.
 The columns are labeled with the headings "Res", "Position", and Roman Numerals

I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 6, and Table 7: "Res": amino acid residue of SEQ ID NO:89 and Figures 4A-4H; "Position": position of the corresponding residue within SEQ ID NO:89 and Figures 4A-4H; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

A clone (HOHCA60) containing all or most of the sequence for SEQ ID NO:18 was deposited with the American Type Culture Collection ("ATCC") on September 7, 1999, and was given the ATCC Deposit Number PTA-627. The ATCC is located at 10801 University Boulevard, Manassas, VA 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure. Clone HOHCA60 was isolated from a osteoblast II cDNA library. This clone contains the entire coding region identified as SEQ ID NO:18. The deposited clone contains a cDNA having a total of 5720 nucleotides, which encodes a predicted open reading frame of 1745 amino acid residues. (See Figure 4A-4H.) The open reading frame begins at a N-terminal methionine located at nucleotide position 67, and ends at a stop codon at nucleotide position 5302. The predicted molecular weight of the THRAP protein is about 191 kDa.

Subsequent Northern analysis also showed that this gene is expressed primarily in testes, fetal tissue (e.g., lung, heart), synovial sarcoma, brain, immune cells and tissues (e. g., lymph node, macrophage), colon, prostate, small intestine, thyroid and to a lesser extent in many other tissues.

DOMAINS: It has also been discovered that THRAP (SEQ ID NO:89) contains 13 TSP-1-like domains, an IgG-like domain, and a proteinase inhibitor-like domain. More particularly, (a) a predicted TSP-1-like domain1 (SEQ ID NO:161)

located at about amino acids 33 to 82 of SEQ ID NO:89; (b) a predicted TSP-1-like domain2 (SEQ ID NO:162) located at about amino acids 301-360 of SEQ ID NO:89; (c) a predicted TSP-1-like domain3 (SEQ ID NO:163) located at about amino acids 363-421 of SEQ ID NO:89, (d) a predicted TSP-1-like domain4 (SEQ ID NO:164) located at about amino acids 423-475 of SEQ ID NO:89, (e) a predicted TSP-1-like domain5 (SEQ ID NO:165) located at about amino acids 514-566 of SEQ ID NO:89, (f) a predicted TSP-1-like domain6 (SEQ ID NO:166) located at about amino acids 590-650 of SEQ ID NO:89, (g) a predicted TSP-1-like domain7 (SEQ ID NO:167) located at about amino acids 653-712 SEQ ID NO:89, (h) a predicted TSP-1-like domain8 (SEQ ID NO:168) located at about amino acids 715-772 of SEQ ID NO:89, (i) a predicted TSP-1-like domain9 (SEQ ID NO:169) located at about amino acids 775-832 of SEQ ID NO:89, (j) a predicted TSP-1-like domain10 (SEQ ID NO:170) located at about amino acids 1473-1529 SEQ ID NO:89, (k) a predicted TSP-1-like domain11 (SEQ ID NO:171) located at about amino acids 1532-1590 of SEQ ID NO:89, (l) a predicted TSP-1-like domain12 (SEQ ID NO:172) located at about amino acids 1593-1650 of SEQ ID NO:89, (m) a predicted TSP-1-like domain13 (SEQ ID NO:173) located at about amino acids 1653-1708 SEQ ID NO:89, (n) a predicted proteinase inhibitor domain (SEQ ID NO:174) located at about amino acids 83-220 of SEQ ID NO:89, and (o) a predicted IgG-like domain (SEQ ID NO:175) located at about amino acids 1180-1471 of SEQ ID NO:89. In this context "about" includes the particularly recited ranges, larger or smaller by several (10, 9, 8, 7, 6, 5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. These polypeptide fragments of THRAP are specifically contemplated in the present invention.

25 SIGNAL SEQUENCE. Moreover, the encoded polypeptide has a THRAP leader sequence located at about amino acids 1-28. (See Figure 4A-4H.) Also shown in Figure 4A-4H, the THRAP secreted protein encompasses about amino acid residues 29-1745. In this context "about" includes the particularly recited ranges, larger or smaller by several (10, 9, 8, 7, 6, 5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. These polypeptide fragments of THRAP are specifically contemplated in the present invention.

N-terminal deletions of the THRAP polypeptide can be described by the general formula m-1745, where m is an integer from 2 to 1739 where m corresponds to the position of the amino acid residue identified in SEQ ID NO:89. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: E-2 to A-1745; C-3 to A-1745; C-4 to A-1745; R-5 to A-1745; R-6 to A-1745; A-7 to A-1745; T-8 to A-1745; P-9 to A-1745; G-10 to A-1745; T-11 to A-1745; L-12 to A-1745; L-13 to A-1745; L-14 to A-1745; F-15 to A-1745; L-16 to A-1745; A-17 to A-1745; F-18 to A-1745; L-19 to A-1745; L-20 to A-1745; L-21 to A-1745; S-22 to A-1745; S-23 to A-1745; R-24 to A-1745; T-25 to A-1745; A-26 to A-1745; R-27 to A-1745; S-28 to A-1745; E-29 to A-1745; E-30 to A-1745; D-31 to A-1745; R-32 to A-1745; D-33 to A-1745; G-34 to A-1745; L-35 to A-1745; W-36 to A-1745; D-37 to A-1745; A-38 to A-1745; W-39 to A-1745; G-40 to A-1745; P-41 to A-1745; W-42 to A-1745; S-43 to A-1745; E-44 to A-1745; C-45 to A-1745; S-46 to A-1745; R-47 to A-1745; T-48 to A-1745; C-49 to A-1745; G-50 to A-1745; G-51 to A-1745; G-52 to A-1745; A-53 to A-1745; S-54 to A-1745; Y-55 to A-1745; S-56 to A-1745; L-57 to A-1745; R-58 to A-1745; R-59 to A-1745; C-60 to A-1745; L-61 to A-1745; S-62 to A-1745; S-63 to A-1745; K-64 to A-1745; S-65 to A-1745; C-66 to A-1745; E-67 to A-1745; G-68 to A-1745; R-69 to A-1745; N-70 to A-1745; I-71 to A-1745; R-72 to A-1745; Y-73 to A-1745; R-74 to A-1745; T-75 to A-1745; C-76 to A-1745; S-77 to A-1745; N-78 to A-1745; V-79 to A-1745; D-80 to A-1745; C-81 to A-1745; P-82 to A-1745; P-83 to A-1745; E-84 to A-1745; A-85 to A-1745; G-86 to A-1745; D-87 to A-1745; F-88 to A-1745; R-89 to A-1745; A-90 to A-1745; Q-91 to A-1745; Q-92 to A-1745; C-93 to A-1745; S-94 to A-1745; A-95 to A-1745; H-96 to A-1745; N-97 to A-1745; D-98 to A-1745; V-99 to A-1745; K-100 to A-1745; H-101 to A-1745; H-102 to A-1745; G-103 to A-1745; Q-104 to A-1745; F-105 to A-1745; Y-106 to A-1745; E-107 to A-1745; W-108 to A-1745; L-109 to A-1745; P-110 to A-1745; V-111 to A-1745; S-112 to A-1745; N-113 to A-1745; D-114 to A-1745; P-115 to A-1745; D-116 to A-1745; N-117 to A-1745; P-118 to A-1745; C-119 to A-1745; S-120 to A-1745; L-121 to A-1745; K-122 to A-1745; C-123 to A-1745; Q-124 to A-1745; A-125 to A-1745; K-126 to A-1745; G-127 to A-1745; T-128 to A-1745; T-129 to A-1745;

L-130 to A-1745; V-131 to A-1745; V-132 to A-1745; E-133 to A-1745; L-134 to A-1745; A-135 to A-1745; P-136 to A-1745; K-137 to A-1745; V-138 to A-1745; L-139 to A-1745; D-140 to A-1745; G-141 to A-1745; T-142 to A-1745; R-143 to A-1745; C-144 to A-1745; Y-145 to A-1745; T-146 to A-1745; E-147 to A-1745; S-148 to A-1745; L-149 to A-1745; D-150 to A-1745; M-151 to A-1745; C-152 to A-1745; I-153 to A-1745; S-154 to A-1745; G-155 to A-1745; L-156 to A-1745; C-157 to A-1745; Q-158 to A-1745; I-159 to A-1745; V-160 to A-1745; G-161 to A-1745; C-162 to A-1745; D-163 to A-1745; H-164 to A-1745; Q-165 to A-1745; L-166 to A-1745; G-167 to A-1745; S-168 to A-1745; T-169 to A-1745; V-170 to A-1745; K-171 to A-1745; E-172 to A-1745; D-173 to A-1745; N-174 to A-1745; C-175 to A-1745; G-176 to A-1745; V-177 to A-1745; C-178 to A-1745; N-179 to A-1745; G-180 to A-1745; D-181 to A-1745; G-182 to A-1745; S-183 to A-1745; T-184 to A-1745; C-185 to A-1745; R-186 to A-1745; L-187 to A-1745; V-188 to A-1745; R-189 to A-1745; G-190 to A-1745; Q-191 to A-1745; Y-192 to A-1745; K-193 to A-1745; S-194 to A-1745; Q-195 to A-1745; L-196 to A-1745; S-197 to A-1745; A-198 to A-1745; T-199 to A-1745; K-200 to A-1745; S-201 to A-1745; D-202 to A-1745; D-203 to A-1745; T-204 to A-1745; V-205 to A-1745; V-206 to A-1745; A-207 to A-1745; I-208 to A-1745; P-209 to A-1745; Y-210 to A-1745; G-211 to A-1745; S-212 to A-1745; R-213 to A-1745; H-214 to A-1745; I-215 to A-1745; R-216 to A-1745; L-217 to A-1745; V-218 to A-1745; L-219 to A-1745; K-220 to A-1745; G-221 to A-1745; P-222 to A-1745; D-223 to A-1745; H-224 to A-1745; L-225 to A-1745; Y-226 to A-1745; L-227 to A-1745; E-228 to A-1745; T-229 to A-1745; K-230 to A-1745; T-231 to A-1745; L-232 to A-1745; Q-233 to A-1745; G-234 to A-1745; T-235 to A-1745; K-236 to A-1745; G-237 to A-1745; E-238 to A-1745; N-239 to A-1745; S-240 to A-1745; L-241 to A-1745; S-242 to A-1745; S-243 to A-1745; T-244 to A-1745; G-245 to A-1745; T-246 to A-1745; F-247 to A-1745; L-248 to A-1745; V-249 to A-1745; D-250 to A-1745; N-251 to A-1745; S-252 to A-1745; S-253 to A-1745; V-254 to A-1745; D-255 to A-1745; F-256 to A-1745; Q-257 to A-1745; K-258 to A-1745; F-259 to A-1745; P-260 to A-1745; D-261 to A-1745; K-262 to A-1745; E-263 to A-1745; I-264 to A-1745; L-265 to A-1745; R-266 to A-1745; M-267 to A-1745; A-268 to A-1745; G-269 to A-1745; P-270 to A-1745; L-271 to A-1745; T-272 to A-1745; A-273 to A-1745; D-274 to A-1745; F-275 to A-1745; I-276 to A-1745; V-277 to A-1745; K-278 to A-1745; I-279 to

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to A-1745; Y-592 to A-1745; D-593 to A-1745; W-594 to A-1745; E-595 to A-1745;
5 Y-596 to A-1745; E-597 to A-1745; G-598 to A-1745; F-599 to A-1745; T-600 to A-
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to A-1745; C-606 to A-1745; G-607 to A-1745; G-608 to A-1745; G-609 to A-1745;
V-610 to A-1745; Q-611 to A-1745; E-612 to A-1745; A-613 to A-1745; V-614 to A-
1745; V-615 to A-1745; S-616 to A-1745; C-617 to A-1745; L-618 to A-1745; N-619
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E-624 to A-1745; P-625 to A-1745; A-626 to A-1745; E-627 to A-1745; E-628 to A-
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to A-1745; S-634 to A-1745; R-635 to A-1745; R-636 to A-1745; P-637 to A-1745; P-
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1721 to A-1745; K-1722 to A-1745; V-1723 to A-1745; K-1724 to A-1745; Q-1725 to A-1745; L-1726 to A-1745; K-1727 to A-1745; L-1728 to A-1745; C-1729 to A-1745; Q-1730 to A-1745; L-1731 to A-1745; S-1732 to A-1745; Q-1733 to A-1745; F-1734 to A-1745; K-1735 to A-1745; S-1736 to A-1745; R-1737 to A-1745; C-1738 to A-1745; C-1739 to A-1745; and G-1740 to A-1745 of SEQ ID NO: 89. Polypeptides encoded by these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the THRAP polypeptide shown in Figure 4A-4H (SEQ ID NO:89), as described by the general formula 1-n, where n is an integer from 6 to 1745 where n corresponds to the position of amino acid residue identified in SEQ ID NO:89. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: E-29 to K-1744; E-29 to G-1743; E-29 to C-1742; E-29 to T-1741; E-29 to G-1740; E-29 to C-1739; E-29 to C-1738; E-29 to R-1737; E-29 to S-1736; E-29 to K-1735; E-29 to F-1734; E-29 to Q-1733; E-29 to S-1732; E-29 to L-1731; E-29 to Q-1730; E-29 to C-1729; E-29 to L-1728; E-29 to K-1727; E-29 to L-1726; E-29 to Q-1725; E-29 to K-1724; E-29 to V-1723; E-29 to K-1722; E-29 to E-1721; E-29 to C-1720; E-29 to Y-1719; E-29 to R-1718; E-29 to T-1717; E-29 to T-1716; E-29 to D-1715; E-29 to R-1714; E-29 to C-1713; E-29 to E-1712; E-29 to E-29711; E-29 to N-1710; E-29 to E-1709; E-29 to C-1708; E-29 to P-1707; E-29 to T-1706; E-29 to I-1705; E-29 to N-1704; E-29 to C-1703; E-29 to R-1702; E-29 to Q-1701; E-29 to W-1700; E-29 to N-1699; E-29 to A-1698; E-29 to P-1697; E-29 to R-1696; E-29 to P-1695; E-29 to G-1694; E-29 to W-1693; E-29 to S-1692; E-29 to C-1691; E-29 to L-1690; E-29 to H-1689; E-29 to E-

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10 29 toC-475; E-29 to P-474; E-29 to T-473; E-29 to P-472; E-29 to V-471; E-29 to I-470; E-29to C-469; E-29 to E-468; E-29 to E-467; E-29 to K-466; E-29 to I-465; E-29 to H-464;E-29 to P-463; E-29 to K-462; E-29 to T-461; E-29 to K-460; E-29 to P-459; E-29 toS-458; E-29 to C-457; E-29 to G-456; E-29 to G-455; E-29 to T-454; E-29 to H-453; E-29to M-452; E-29 to G-451; E-29 to R-450; E-29 to H-449; E-29 to
15 D-448; E-29 to I-447;E-29 to C-446; E-29 to L-445; E-29 to V-444; E-29 to V-443; E-29 to R-442; E-29 toY-441; E-29 to R-440; E-29 to L-439; E-29 to G-438; E-29 to Q-437; E-29 to G-436; E-29to C-435; E-29 to T-434; E-29 to V-433; E-29 to T-432; E-29 to C-431; E-29 to P-430;E-29 to S-429; E-29 to W-428; E-29 to E-427; E-29 to Q-426; E-29 to A-425; E-29 toL-424; E-29 to W-423; E-29 to K-422; E-29 to P-421;
20 E-29 to C-420; E-29 to D-419; E-29to F-418; E-29 to I-417; E-29 to N-416; E-29 to C-415; E-29 to P-414; E-29 to Q-413;E-29 to A-412; E-29 to I-411; E-29 to P-410; E-29 to M-409; E-29 to K-408; E-29 toP-407; E-29 to T-406; E-29 to Y-405; E-29 to M-404; E-29 to C-403; E-29 to K-402; E-29to W-401; E-29 to E-400; E-29 to E-399; E-29 to V-398; E-29 to S-397; E-29 to T-396;E-29 to V-395; E-29 to H-394; E-29 to G-393; E-29 to Q-392; E-29 to I-391; E-29 toD-390; E-29 to E-389; E-29 to E-388; E-29 to V-387; E-29 to C-386; E-29 to S-385; E-29to V-384; E-29 to A-383; E-29 to R-382; E-29 to S-381; E-29 to Q-380; E-29 to I-379;E-29 to G-378; E-29 to G-377; E-29 to G-376; E-29 to C-375; E-29 to S-374; E-29 toS-373; E-29 to S-372; E-29 to C-371; E-29 to A-370; E-29 to T-369; E-29 to W-368; E-29to P-367; E-29 to T-366; E-
25 29 to A-365; E-29 to E-364; E-29 to W-363; E-29 to R-362;E-29 to A-361; E-29 to P-360; E-29 to C-359; E-29 to P-358; E-29 to D-357; E-29 toL-356; E-29 to N-355; E-29 to C-354; E-29 to E-353; E-29 to Q-352; E-29 to L-351; E-29to K-350; E-29 to P-

349; E-29 to K-348; E-29 to P-347; E-29 to K-346; E-29 to I-345; E-29 to N-344; E-29 to E-343; E-29 to P-342; E-29 to Y-341; E-29 to Y-340; E-29 to H-339; E-29 to C-338; E-29 to Y-337; E-29 to Q-336; E-29 to D-335; E-29 to A-334; E-29 to V-333; E-29 to V-332; E-29 to R-331; E-29 to N-330; E-29 to S-329; E-29 to R-328; E-29 to L-327; E-29 to D-326; E-29 to Y-325; E-29 to C-324; E-29 to E-323; E-29 to A-322; E-29 to S-321; E-29 to T-320; E-29 to L-319; E-29 to Q-318; E-29 to Y-317; E-29 to G-316; E-29 to G-315; E-29 to G-314; E-29 to C-313; E-29 to T-312; E-29 to A-311; E-29 to S-310; E-29 to C-309; E-29 to P-308; E-29 to F-307; E-29 to F-306; E-29 to D-305; E-29 to T-304; E-29 to E-303; E-29 to R-302; E-29 to W-301; E-29 to R-300; E-29 to H-299; E-29 to I-298; E-29 to I-297; E-29 to P-296; E-29 to Q-295; E-29 to Y-294; E-29 to F-293; E-29 to I-292; E-29 to F-291; E-29 to Q-290; E-29 to V-289; E-29 to T-288; E-29 to S-287; E-29 to D-286; E-29 to A-285; E-29 to S-284; E-29 to G-283; E-29 to S-282; E-29 to N-281; E-29 to R-280; E-29 to I-279; E-29 to K-278; E-29 to V-277; E-29 to I-276; E-29 to F-275; E-29 to D-274; E-29 to A-273; E-29 to T-272; E-29 to L-271; E-29 to P-270; E-29 to G-269; E-29 to A-268; E-29 to M-267; E-29 to R-266; E-29 to L-265; E-29 to I-264; E-29 to E-263; E-29 to K-262; E-29 to D-261; E-29 to P-260; E-29 to F-259; E-29 to K-258; E-29 to Q-257; E-29 to F-256; E-29 to D-255; E-29 to V-254; E-29 to S-253; E-29 to S-252; E-29 to N-251; E-29 to D-250; E-29 to V-249; E-29 to L-248; E-29 to F-247; E-29 to T-246; E-29 to G-245; E-29 to T-244; E-29 to S-243; E-29 to S-242; E-29 to L-241; E-29 to S-240; E-29 to N-239; E-29 to E-238; E-29 to G-237; E-29 to K-236; E-29 to T-235; E-29 to G-234; E-29 to Q-233; E-29 to L-232; E-29 to T-231; E-29 to K-230; E-29 to T-229; E-29 to E-228; E-29 to L-227; E-29 to Y-226; E-29 to L-225; E-29 to H-224; E-29 to D-223; E-29 to P-222; E-29 to G-221; E-29 to K-220; E-29 to L-219; E-29 to V-218; E-29 to L-217; E-29 to R-216; E-29 to I-215; E-29 to H-214; E-29 to R-213; E-29 to S-212; E-29 to G-211; E-29 to Y-210; E-29 to P-209; E-29 to I-208; E-29 to A-207; E-29 to V-206; E-29 to V-205; E-29 to T-204; E-29 to D-203; E-29 to D-202; E-29 to S-201; E-29 to K-200; E-29 to T-199; E-29 to A-198; E-29 to S-197; E-29 to L-196; E-29 to Q-195; E-29 to S-194; E-29 to K-193; E-29 to Y-192; E-29 to Q-191; E-29 to G-190; E-29 to R-189; E-29 to V-188; E-29 to L-187; E-29 to R-186; E-29 to C-185; E-29 to T-184; E-29 to S-183; E-29 to G-182; E-29 to D-181; E-29 to G-180; E-29 to N-179; E-29 to C-178; E-29 to V-177; E-29 to G-176; E-29 to C-175; E-29 to N-174; E-29 to D-173; E-

29 to E-172; E-29 to K-171; E-29 to V-170; E-29 to T-169; E-29 to S-168; E-29 to G-167; E-29 to L-166; E-29 to Q-165; E-29 to H-164; E-29 to D-163; E-29 to C-162; E-29 to G-161; E-29 to V-160; E-29 to I-159; E-29 to Q-158; E-29 to C-157; E-29 to L-156; E-29 to G-155; E-29 to S-154; E-29 to I-153; E-29 to C-152; E-29 to E-2951; E-29 to D-150; E-29 to L-149; E-29 to S-148; E-29 to E-147; E-29 to T-146; E-29 to Y-145; E-29 to C-144; E-29 to R-143; E-29 to T-142; E-29 to G-141; E-29 to D-140; E-29 to L-139; E-29 to V-138; E-29 to K-137; E-29 to P-136; E-29 to A-135; E-29 to L-134; E-29 to E-133; E-29 to V-132; E-29 to V-131; E-29 to L-130; E-29 to T-129; E-29 to T-128; E-29 to G-127; E-29 to K-126; E-29 to A-125; E-29 to Q-124; E-29 to C-123; E-29 to K-122; E-29 to L-121; E-29 to S-120; E-29 to C-119; E-29 to P-118; E-29 to N-117; E-29 to D-116; E-29 to P-115; E-29 to D-114; E-29 to N-113; E-29 to S-112; E-29 to V-111; E-29 to P-110; E-29 to L-109; E-29 to W-108; E-29 to E-107; E-29 to Y-106; E-29 to F-105; E-29 to Q-104; E-29 to G-103; E-29 to H-102; E-29 to H-101; E-29 to K-100; E-29 to V-99; E-29 to D-98; E-29 to N-97; E-29 to H-96; E-29 to A-95; E-29 to S-94; E-29 to C-93; E-29 to Q-92; E-29 to Q-91; E-29 to A-90; E-29 to R-89; E-29 to F-88; E-29 to D-87; E-29 to G-86; E-29 to A-85; E-29 to E-84; E-29 to P-83; E-29 to P-82; E-29 to C-81; E-29 to D-80; E-29 to V-79; E-29 to N-78; E-29 to S-77; E-29 to C-76; E-29 to T-75; E-29 to R-74; E-29 to Y-73; E-29 to R-72; E-29 to I-71; E-29 to N-70; E-29 to R-69; E-29 to G-68; E-29 to E-67; E-29 to C-66; E-29 to S-65; E-29 to K-64; E-29 to S-63; E-29 to S-62; E-29 to L-61; E-29 to C-60; E-29 to R-59; E-29 to R-58; E-29 to L-57; E-29 to S-56; E-29 to Y-55; E-29 to S-54; E-29 to A-53; E-29 to G-52; E-29 to G-51; E-29 to G-50; E-29 to C-49; E-29 to T-48; E-29 to R-47; E-29 to S-46; E-29 to C-45; E-29 to E-44; E-29 to S-43; E-29 to W-42; E-29 to P-41; E-29 to G-40; E-29 to W-39; E-29 to A-38; E-29 to D-37; E-29 to W-36; E-29 to L-35; E-29 to G-34; E-29 to D-33; E-29 to R-32; E-29 to D-31; or E-29 to E-30 of SEQ ID NO:89. Polypeptides encoded by these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the

invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Moreover, a signal sequence may be added to these C-terminal constructs. For example, amino acids 1-28 of SEQ ID NO:89, amino acids 2-28 of SEQ ID NO:89, amino acids 3-28 of SEQ ID NO:89, amino acids 4-28 of SEQ ID NO:89, amino acids 5-28 of SEQ ID NO:89, amino acids 6-28 of SEQ ID NO:89, amino acids 7-28 of SEQ ID NO:89, amino acids 8-28 of SEQ ID NO:89, amino acids 9-28 of SEQ ID NO:89, amino acids 10-28 of SEQ ID NO:89, amino acids 11-28 of SEQ ID NO:89, amino acids 12-28 of SEQ ID NO:89, amino acids 13-28 of SEQ ID NO:89, amino acids 14-28 of SEQ ID NO:89, amino acids 15-28 of SEQ ID NO:89, amino acids 16-28 of SEQ ID NO:89, amino acids 17-28 of SEQ ID NO:89, amino acids 18-28 of SEQ ID NO:89, amino acids 19-28 of SEQ ID NO:89, amino acids 20-28 of SEQ ID NO:89, amino acids 21-28 of SEQ ID NO:89, amino acids 22-28 of SEQ ID NO:89, amino acids 23-28 of SEQ ID NO:89, amino acids 24-28 of SEQ ID NO:89, amino acids 25-28 of SEQ ID NO:89, amino acids 26-28 of SEQ ID NO:89, or amino acids 27-28 of SEQ ID NO:89 can be added to the N-terminus of each C-terminal constructs listed above.

In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted THRAP polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO:89, where n and m are integers as described above. It is understood, however, that any N- and C- terminal deletion mutant is at least, preferably, 6 amino acids, 10 amino acids, 20 amino acids, or 50 amino acids in length. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Moreover, the invention provides nucleic acid molecules having nucleotide sequences related to extensive portions of SEQ ID NO:18 which have been determined from the following related cDNA clones: HBINE55R (SEQ ID NO:156), HOEEW19R (SEQ ID NO:157), HSLAS01R (SEQ ID NO:158), HORBP08R (SEQ ID NO:159) and HAJBI67R (SEQ ID NO:160).

Also preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: TSP-1-like domain1; TSP-1-like domain1 and the proteinase domain; TSP-1-like domain1, the proteinase domain, and the TSP-1-like domain2; TSP-1-like domain1, the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain3; TSP-1-like domain1, the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain4; TSP-1-like domain1, the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain5; TSP-1-like domain1, the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain6; TSP-1-like domain1, the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain7; TSP-1-like domain1, the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain8; TSP-1-like domain1, the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain9; TSP-1-like domain1, the proteinase domain, the TSP-1-like domain2 to TSP-1-like domain9, and the IgG-like domain; TSP-1-like domain1, the proteinase domain, the TSP-1-like domain2 to TSP-1-like domain9, the IgG-like domain and the TSP-1-like domain10; TSP-1-like domain1, the proteinase domain, the TSP-1-like domain2 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 and the TSP-1-like domain11; TSP-1-like domain1, the proteinase domain, the TSP-1-like domain2 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 to the TSP-1-like domain12; or TSP-1-like domain1, the proteinase domain, the TSP-1-like domain2 to TSP-1-like domain9, the IgG-like domain, and the TSP-1-like domain10 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: the proteinase domain; the proteinase domain, and the TSP-1-like domain2; the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain3; the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain4; the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain5; the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain6; the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain7; the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain8; the proteinase domain, and the TSP-1-like domain2 to TSP-1-like domain9; the proteinase domain, the TSP-1-like domain2 to TSP-1-like domain9, and the IgG-like domain; the proteinase domain, the TSP-1-like domain2 to TSP-1-like domain9, the

IgG-like domain and the TSP-1-like domain10; the proteinase domain, the TSP-1-like domain2 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 and the TSP-1-like domain11; the proteinase domain, the TSP-1-like domain2 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 to the TSP-1-like domain12; or the proteinase domain, the TSP-1-like domain2 to TSP-1-like domain9, the IgG-like domain, and the TSP-1-like domain10 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: TSP-1-like domain2; the TSP-1-like domain2 to TSP-1-like domain3; the TSP-1-like domain2 to TSP-1-like domain4; the TSP-1-like domain2 to TSP-1-like domain5; the TSP-1-like domain2 to TSP-1-like domain6; the TSP-1-like domain2 to TSP-1-like domain7; the TSP-1-like domain2 to TSP-1-like domain8; the TSP-1-like domain2 to TSP-1-like domain9; the TSP-1-like domain2 to TSP-1-like domain9, and the IgG-like domain; the TSP-1-like domain2 to TSP-1-like domain9, the IgG-like domain and the TSP-1-like domain10; the TSP-1-like domain2 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 and the TSP-1-like domain11; the TSP-1-like domain2 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 to the TSP-1-like domain12; or the TSP-1-like domain2 to TSP-1-like domain9, the IgG-like domain, and the TSP-1-like domain10 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: the TSP-1-like domain3; the TSP-1-like domain3 to TSP-1-like domain4; the TSP-1-like domain3 to TSP-1-like domain5; the TSP-1-like domain3 to TSP-1-like domain6; the TSP-1-like domain3 to TSP-1-like domain7; the TSP-1-like domain3 to TSP-1-like domain8; the TSP-1-like domain3 to TSP-1-like domain9; the TSP-1-like domain3 to TSP-1-like domain9, and the IgG-like domain; the TSP-1-like domain3 to TSP-1-like domain9, the IgG-like domain and the TSP-1-like domain10; the TSP-1-like domain3 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 and the TSP-1-like domain11; the TSP-1-like domain3 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 to the TSP-1-like domain12; or the TSP-1-like domain3 to TSP-1-like domain9, the IgG-like domain, and the TSP-1-like domain10 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: the TSP-1-like domain4; the TSP-1-like domain4 to TSP-1-like domain5; the TSP-1-like domain4 to TSP-1-like domain6; the TSP-1-like domain4 to TSP-1-like domain7; the TSP-1-like domain4 to TSP-1-like domain8; 5 the TSP-1-like domain4 to TSP-1-like domain9; the TSP-1-like domain4 to TSP-1-like domain9, and the IgG-like domain; the TSP-1-like domain4 to TSP-1-like domain9, the IgG-like domain and the TSP-1-like domain10; the TSP-1-like domain4 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 and the TSP-1-like domain11; the TSP-1-like domain4 to TSP-1-like domain9, the IgG-like 10 domain, the TSP-1-like domain10 to the TSP-1-like domain12; or the TSP-1-like domain4 to TSP-1-like domain9, the IgG-like domain, and the TSP-1-like domain10 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: the TSP-1-like domain5; the TSP-1-like domain5 15 to TSP-1-like domain6; the TSP-1-like domain5 to TSP-1-like domain7; the TSP-1-like domain5 to TSP-1-like domain8; the TSP-1-like domain5 to TSP-1-like domain9; the TSP-1-like domain5 to TSP-1-like domain9, and the IgG-like domain; the TSP-1-like domain5 to TSP-1-like domain9, the IgG-like domain and the TSP-1-like domain10; the TSP-1-like domain5 to TSP-1-like domain9, the IgG-like domain, the 20 TSP-1-like domain10 and the TSP-1-like domain11; the TSP-1-like domain5 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 to the TSP-1-like domain12; or the TSP-1-like domain5 to TSP-1-like domain9, the IgG-like domain, and the TSP-1-like domain10 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or 25 consist of, the following fragments: the TSP-1-like domain6; the TSP-1-like domain6 to TSP-1-like domain7; the TSP-1-like domain6 to TSP-1-like domain8; the TSP-1-like domain6 to TSP-1-like domain9; the TSP-1-like domain6 to TSP-1-like domain9, and the IgG-like domain; the TSP-1-like domain6 to TSP-1-like domain9, the IgG-like domain and the TSP-1-like domain10; the TSP-1-like domain6 to TSP-1-like 30 domain9, the IgG-like domain, the TSP-1-like domain10 and the TSP-1-like domain11; the TSP-1-like domain6 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 to the TSP-1-like domain12; or the TSP-1-like domain6 to TSP-

1-like domain9, the IgG-like domain, and the TSP-1-like domain10 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: the TSP-1-like domain7; the TSP-1-like domain7 to TSP-1-like domain8; the TSP-1-like domain7 to TSP-1-like domain9; the TSP-1-like domain7 to TSP-1-like domain9, and the IgG-like domain; the TSP-1-like domain7 to TSP-1-like domain9, the IgG-like domain and the TSP-1-like domain10; the TSP-1-like domain7 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 and the TSP-1-like domain11; the TSP-1-like domain7 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 to the TSP-1-like domain12; or the TSP-1-like domain7 to TSP-1-like domain9, the IgG-like domain, and the TSP-1-like domain10 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: the TSP-1-like domain8; the TSP-1-like domain8 to TSP-1-like domain9; the TSP-1-like domain8 to TSP-1-like domain9, and the IgG-like domain; the TSP-1-like domain8 to TSP-1-like domain9, the IgG-like domain and the TSP-1-like domain10; the TSP-1-like domain8 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 and the TSP-1-like domain11; the TSP-1-like domain8 to TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 to the TSP-1-like domain12; or the TSP-1-like domain8 to TSP-1-like domain9, the IgG-like domain, and the TSP-1-like domain10 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: the TSP-1-like domain9; TSP-1-like domain9 and the IgG-like domain; the TSP-1-like domain9, the IgG-like domain and the TSP-1-like domain10; the TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 and the TSP-1-like domain11; the TSP-1-like domain9, the IgG-like domain, the TSP-1-like domain10 to the TSP-1-like domain12; or the TSP-1-like domain9, the IgG-like domain, and the TSP-1-like domain10 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: the IgG-like domain; the IgG-like domain and the TSP-1-like domain10; the IgG-like domain, the TSP-1-like domain10 and the TSP-1-like domain11; the IgG-like domain, the TSP-1-like domain10 to the TSP-1-like

domain12; or the IgG-like domain, and the TSP-1-like domain10 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: the TSP-1-like domain10; the TSP-1-like domain10 and the TSP-1-like domain11; the TSP-1-like domain10 to the TSP-1-like domain12; and the TSP-1-like domain10 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: the TSP-1-like domain11; the TSP-1-like domain11 to the TSP-1-like domain12; and the TSP-1-like domain11 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragment: the TSP-1-like domain12; or the TSP-1-like domain12 to the TSP-1-like domain13.

Additionally, preferred polypeptide fragments of the invention comprise, or consist of, the following fragments: the TSP-1-like domain13.

Also included are a nucleotide sequence encoding a polypeptide consisting of a portion of the complete THRAP amino acid sequence encoded by the cDNA clone (HOHCA60) contained in ATCC Deposit No. PTA-627, where this portion excludes any integer of amino acid residues from 1 to about 1735 amino acids from the amino terminus of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-627, or any integer of amino acid residues from 1 to about 1735 amino acids from the carboxy terminus, or any combination of the above amino terminal and carboxy terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-627. Polynucleotides encoding all of the above deletion mutant polypeptide forms are also encompassed by the invention.

In additional embodiments, the polynucleotides of the invention encode functional attributes of THRAP. Preferred embodiments of the invention in this regard include fragments that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta

amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions of THRAP.

The data representing the structural or functional attributes of THRAP set forth in Figure 4A-4H and/or Table 7, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 7 can be used to determine regions of THRAP which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or IV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 4A-H, and Table 7: "Res": amino acid residue of SEQ ID NO: 89 and Figures 4A-4H; "Position": position of the corresponding residue within SEQ ID NO: 89 and Figures 4A-4H; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

Certain preferred regions in these regards are set out in Figure 6, but may, as shown in Table 7, be represented or identified by using tabular representations of the data presented in Figure 6. The DNA*STAR computer algorithm used to generate Figure 6 (set on the original default parameters) was used to present the data in Figure 6 in a tabular format (See Table 7). The tabular format of the data in Figure 6 may be used to easily determine specific boundaries of a preferred region.

The above-mentioned preferred regions set out in Figure 6 and in Table 7 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in Figure 4A-4H. As set out in Figure 6

and in Table 7, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and coil-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index.

Also preferred are THRAP polypeptide variants. For example, site directed changes at the amino acid level of THRAP (SEQ ID NO:89) can be made by replacing a particular amino acid with a conservative amino acid. Preferred conservative substitutions include: M1 replaced with A, G, I, L, S, T, or V; E2 replaced with D; R5 replaced with H, or K; R6 replaced with H, or K; A7 replaced with G, I, L, S, T, M, or V; T8 replaced with A, G, I, L, S, M, or V; G10 replaced with A, I, L, S, T, M, or V; T11 replaced with A, G, I, L, S, M, or V; L12 replaced with A, G, I, S, T, M, or V; L13 replaced with A, G, I, S, T, M, or V; L14 replaced with A, G, I, S, T, M, or V; F15 replaced with W, or Y; L16 replaced with A, G, I, S, T, M, or V; A17 replaced with G, I, L, S, T, M, or V; F18 replaced with W, or Y; L19 replaced with A, G, I, S, T, M, or V; L20 replaced with A, G, I, S, T, M, or V; L21 replaced with A, G, I, S, T, M, or V; S22 replaced with A, G, I, L, T, M, or V; S23 replaced with A, G, I, L, T, M, or V; R24 replaced with H, or K; T25 replaced with A, G, I, L, S, M, or V; A26 replaced with G, I, L, S, T, M, or V; R27 replaced with H, or K; S28 replaced with A, G, I, L, T, M, or V; E29 replaced with D; E30 replaced with D; D31 replaced with E; R32 replaced with H, or K; D33 replaced with E; G34 replaced with A, I, L, S, T, M, or V; L35 replaced with A, G, I, S, T, M, or V; W36 replaced with F, or Y; D37 replaced with E; A38 replaced with G, I, L, S, T, M, or V; W39 replaced with F, or Y; G40 replaced with A, I, L, S, T, M, or V; W42 replaced with F, or Y; S43 replaced with A, G, I, L, T, M, or V; E44 replaced with D; S46 replaced with A, G, I, L, T, M, or V; R47 replaced with H, or K; T48 replaced with A, G, I, L, S, M, or V; G50 replaced with A, I, L, S, T, M, or V; G51 replaced with A, I, L, S, T, M, or V; G52 replaced with A, I, L, S, T, M, or V; A53 replaced with G, I, L, S, T, M, or V; S54 replaced with A, G, I, L, T, M, or V; Y55 replaced with F, or W; S56 replaced with A, G, I, L, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; R58 replaced with H, or K; R59 replaced with H, or K; L61 replaced with A, G, I, S, T, M, or V;

S62 replaced with A, G, I, L, T, M, or V; S63 replaced with A, G, I, L, T, M, or V;
 K64 replaced with H, or R; S65 replaced with A, G, I, L, T, M, or V; E67 replaced
 with D; G68 replaced with A, I, L, S, T, M, or V; R69 replaced with H, or K; N70
 replaced with Q; I71 replaced with A, G, L, S, T, M, or V; R72 replaced with H, or K;
 5 Y73 replaced with F, or W; R74 replaced with H, or K; T75 replaced with A, G, I, L,
 S, M, or V; S77 replaced with A, G, I, L, T, M, or V; N78 replaced with Q; V79
 replaced with A, G, I, L, S, T, or M; D80 replaced with E; E84 replaced with D; A85
 replaced with G, I, L, S, T, M, or V; G86 replaced with A, I, L, S, T, M, or V; D87
 replaced with E; F88 replaced with W, or Y; R89 replaced with H, or K; A90 replaced
 10 with G, I, L, S, T, M, or V; Q91 replaced with N; Q92 replaced with N; S94 replaced
 with A, G, I, L, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; H96 replaced
 with K, or R; N97 replaced with Q; D98 replaced with E; V99 replaced with A, G, I,
 L, S, T, or M; K100 replaced with H, or R; H101 replaced with K, or R; H102
 replaced with K, or R; G103 replaced with A, I, L, S, T, M, or V; Q104 replaced with
 15 N; F105 replaced with W, or Y; Y106 replaced with F, or W; E107 replaced with D;
 W108 replaced with F, or Y; L109 replaced with A, G, I, S, T, M, or V; V111 replaced
 with A, G, I, L, S, T, or M; S112 replaced with A, G, I, L, T, M, or V; N113 replaced
 with Q; D114 replaced with E; D116 replaced with E; N117 replaced with Q; S120
 replaced with A, G, I, L, T, M, or V; L121 replaced with A, G, I, S, T, M, or V; K122
 20 replaced with H, or R; Q124 replaced with N; A125 replaced with G, I, L, S, T, M, or
 V; K126 replaced with H, or R; G127 replaced with A, I, L, S, T, M, or V; T128
 replaced with A, G, I, L, S, M, or V; T129 replaced with A, G, I, L, S, M, or V; L130
 replaced with A, G, I, S, T, M, or V; V131 replaced with A, G, I, L, S, T, or M; V132
 replaced with A, G, I, L, S, T, or M; E133 replaced with D; L134 replaced with A, G,
 25 I, S, T, M, or V; A135 replaced with G, I, L, S, T, M, or V; K137 replaced with H, or
 R; V138 replaced with A, G, I, L, S, T, or M; L139 replaced with A, G, I, S, T, M, or
 V; D140 replaced with E; G141 replaced with A, I, L, S, T, M, or V; T142 replaced
 with A, G, I, L, S, M, or V; R143 replaced with H, or K; Y145 replaced with F, or W;
 T146 replaced with A, G, I, L, S, M, or V; E147 replaced with D; S148 replaced with
 30 A, G, I, L, T, M, or V; L149 replaced with A, G, I, S, T, M, or V; D150 replaced with
 E; M151 replaced with A, G, I, L, S, T, or V; I153 replaced with A, G, L, S, T, M, or
 V; S154 replaced with A, G, I, L, T, M, or V; G155 replaced with A, I, L, S, T, M, or

V; L156 replaced with A, G, I, S, T, M, or V; Q158 replaced with N; I159 replaced
 with A, G, L, S, T, M, or V; V160 replaced with A, G, I, L, S, T, or M; G161 replaced
 with A, I, L, S, T, M, or V; D163 replaced with E; H164 replaced with K, or R;
 Q165 replaced with N; L166 replaced with A, G, I, S, T, M, or V; G167 replaced with
 5 A, I, L, S, T, M, or V; S168 replaced with A, G, I, L, T, M, or V; T169 replaced with
 A, G, I, L, S, M, or V; V170 replaced with A, G, I, L, S, T, or M; K171 replaced with
 H, or R; E172 replaced with D; D173 replaced with E; N174 replaced with Q;
 G176 replaced with A, I, L, S, T, M, or V; V177 replaced with A, G, I, L, S, T, or M;
 N179 replaced with Q; G180 replaced with A, I, L, S, T, M, or V; D181 replaced with
 10 E; G182 replaced with A, I, L, S, T, M, or V; S183 replaced with A, G, I, L, T, M, or
 V; T184 replaced with A, G, I, L, S, M, or V; R186 replaced with H, or K;
 L187 replaced with A, G, I, S, T, M, or V; V188 replaced with A, G, I, L, S, T, or M;
 R189 replaced with H, or K; G190 replaced with A, I, L, S, T, M, or V; Q191 replaced
 with N; Y192 replaced with F, or W; K193 replaced with H, or R; S194 replaced with
 15 A, G, I, L, T, M, or V; Q195 replaced with N; L196 replaced with A, G, I, S, T, M, or
 V; S197 replaced with A, G, I, L, T, M, or V; A198 replaced with G, I, L, S, T, M, or
 V; T199 replaced with A, G, I, L, S, M, or V; K200 replaced with H, or R; S201
 replaced with A, G, I, L, T, M, or V; D202 replaced with E; D203 replaced with E;
 T204 replaced with A, G, I, L, S, M, or V; V205 replaced with A, G, I, L, S, T, or M;
 20 V206 replaced with A, G, I, L, S, T, or M; A207 replaced with G, I, L, S, T, M, or V;
 I208 replaced with A, G, L, S, T, M, or V; Y210 replaced with F, or W; G211 replaced
 with A, I, L, S, T, M, or V; S212 replaced with A, G, I, L, T, M, or V; R213 replaced
 with H, or K; H214 replaced with K, or R; I215 replaced with A, G, L, S, T, M, or V;
 R216 replaced with H, or K; L217 replaced with A, G, I, S, T, M, or V; V218 replaced
 25 with A, G, I, L, S, T, or M; L219 replaced with A, G, I, S, T, M, or V; K220 replaced
 with H, or R; G221 replaced with A, I, L, S, T, M, or V; D223 replaced with E; H224
 replaced with K, or R; L225 replaced with A, G, I, S, T, M, or V; Y226 replaced with
 F, or W; L227 replaced with A, G, I, S, T, M, or V; E228 replaced with D; T229
 replaced with A, G, I, L, S, M, or V; K230 replaced with H, or R; T231 replaced with
 30 A, G, I, L, S, M, or V; L232 replaced with A, G, I, S, T, M, or V; Q233 replaced with
 N; G234 replaced with A, I, L, S, T, M, or V; T235 replaced with A, G, I, L, S, M, or
 V; K236 replaced with H, or R; G237 replaced with A, I, L, S, T, M, or V; E238

replaced with D; N239 replaced with Q; S240 replaced with A, G, I, L, T, M, or V;
 L241 replaced with A, G, I, S, T, M, or V; S242 replaced with A, G, I, L, T, M, or V;
 S243 replaced with A, G, I, L, T, M, or V; T244 replaced with A, G, I, L, S, M, or V;
 G245 replaced with A, I, L, S, T, M, or V; T246 replaced with A, G, I, L, S, M, or V;
 5 F247 replaced with W, or Y; L248 replaced with A, G, I, S, T, M, or V; V249 replaced
 with A, G, I, L, S, T, or M; D250 replaced with E; N251 replaced with Q; S252
 replaced with A, G, I, L, T, M, or V; S253 replaced with A, G, I, L, T, M, or V; V254
 replaced with A, G, I, L, S, T, or M; D255 replaced with E; F256 replaced with W, or
 Y; Q257 replaced with N; K258 replaced with H, or R; F259 replaced with W, or Y;
 10 D261 replaced with E; K262 replaced with H, or R; E263 replaced with D; I264
 replaced with A, G, L, S, T, M, or V; L265 replaced with A, G, I, S, T, M, or V; R266
 replaced with H, or K; M267 replaced with A, G, I, L, S, T, or V; A268 replaced with
 G, I, L, S, T, M, or V; G269 replaced with A, I, L, S, T, M, or V; L271 replaced with
 A, G, I, S, T, M, or V; T272 replaced with A, G, I, L, S, M, or V; A273 replaced with
 15 G, I, L, S, T, M, or V; D274 replaced with E; F275 replaced with W, or Y; I276
 replaced with A, G, L, S, T, M, or V; V277 replaced with A, G, I, L, S, T, or M; K278
 replaced with H, or R; I279 replaced with A, G, L, S, T, M, or V; R280 replaced with
 H, or K; N281 replaced with Q; S282 replaced with A, G, I, L, T, M, or V; G283
 replaced with A, I, L, S, T, M, or V; S284 replaced with A, G, I, L, T, M, or V; A285
 20 replaced with G, I, L, S, T, M, or V; D286 replaced with E; S287 replaced with A, G,
 I, L, T, M, or V; T288 replaced with A, G, I, L, S, M, or V; V289 replaced with A, G,
 I, L, S, T, or M; Q290 replaced with N; F291 replaced with W, or Y; I292 replaced
 with A, G, L, S, T, M, or V; F293 replaced with W, or Y; Y294 replaced with F, or W;
 Q295 replaced with N; I297 replaced with A, G, L, S, T, M, or V; I298 replaced with
 25 A, G, L, S, T, M, or V; H299 replaced with K, or R; R300 replaced with H, or K;
 W301 replaced with F, or Y; R302 replaced with H, or K; E303 replaced with D; T304
 replaced with A, G, I, L, S, M, or V; D305 replaced with E; F306 replaced with W, or
 Y; F307 replaced with W, or Y; S310 replaced with A, G, I, L, T, M, or V; A311
 replaced with G, I, L, S, T, M, or V; T312 replaced with A, G, I, L, S, M, or V; G314
 30 replaced with A, I, L, S, T, M, or V; G315 replaced with A, I, L, S, T, M, or V; G316
 replaced with A, I, L, S, T, M, or V; Y317 replaced with F, or W; Q318 replaced with
 N; L319 replaced with A, G, I, S, T, M, or V; T320 replaced with A, G, I, L, S, M, or

V; S321 replaced with A, G, I, L, T, M, or V; A322 replaced with G, I, L, S, T, M, or V; E323 replaced with D; Y325 replaced with F, or W; D326 replaced with E; L327 replaced with A, G, I, S, T, M, or V; R328 replaced with H, or K; S329 replaced with A, G, I, L, T, M, or V; N330 replaced with Q; R331 replaced with H, or K; V332 replaced with A, G, I, L, S, T, or M; V333 replaced with A, G, I, L, S, T, or M; A334 replaced with G, I, L, S, T, M, or V; D335 replaced with E; Q336 replaced with N; Y337 replaced with F, or W; H339 replaced with K, or R; Y340 replaced with F, or W; Y341 replaced with F, or W; E343 replaced with D; N344 replaced with Q; I345 replaced with A, G, L, S, T, M, or V; K346 replaced with H, or R; K348 replaced with H, or R; K350 replaced with H, or R; L351 replaced with A, G, I, S, T, M, or V; Q352 replaced with N; E353 replaced with D; N355 replaced with Q; L356 replaced with A, G, I, S, T, M, or V; D357 replaced with E; A361 replaced with G, I, L, S, T, M, or V; R362 replaced with H, or K; W363 replaced with F, or Y; E364 replaced with D; A365 replaced with G, I, L, S, T, M, or V; T366 replaced with A, G, I, L, S, M, or V; W368 replaced with F, or Y; T369 replaced with A, G, I, L, S, M, or V; A370 replaced with G, I, L, S, T, M, or V; S372 replaced with A, G, I, L, T, M, or V; S373 replaced with A, G, I, L, T, M, or V; S374 replaced with A, G, I, L, T, M, or V; G376 replaced with A, I, L, S, T, M, or V; G377 replaced with A, I, L, S, T, M, or V; G378 replaced with A, I, L, S, T, M, or V; I379 replaced with A, G, L, S, T, M, or V; Q380 replaced with N; S381 replaced with A, G, I, L, T, M, or V; R382 replaced with H, or K; A383 replaced with G, I, L, S, T, M, or V; V384 replaced with A, G, I, L, S, T, or M; S385 replaced with A, G, I, L, T, M, or V; V387 replaced with A, G, I, L, S, T, or M; E388 replaced with D; E389 replaced with D; D390 replaced with E; I391 replaced with A, G, L, S, T, M, or V; Q392 replaced with N; G393 replaced with A, I, L, S, T, M, or V; H394 replaced with K, or R; V395 replaced with A, G, I, L, S, T, or M; T396 replaced with A, G, I, L, S, M, or V; S397 replaced with A, G, I, L, T, M, or V; V398 replaced with A, G, I, L, S, T, or M; E399 replaced with D; E400 replaced with D; W401 replaced with F, or Y; K402 replaced with H, or R; M404 replaced with A, G, I, L, S, T, or V; Y405 replaced with F, or W; T406 replaced with A, G, I, L, S, M, or V; K408 replaced with H, or R; M409 replaced with A, G, I, L, S, T, or V; I411 replaced with A, G, L, S, T, M, or V; A412 replaced with G, I, L, S, T, M, or V; Q413 replaced with N; N416 replaced with Q; I417 replaced with A, G, L, S, T, M, or

V;F418 replaced with W, or Y; D419 replaced with E; K422 replaced with H, or R; W423 replaced with F, or Y; L424 replaced with A, G, I, S, T, M, or V; A425 replaced with G, I, L, S, T, M, or V; Q426 replaced with N; E427 replaced with D; W428 replaced with F, or Y; S429 replaced with A, G, I, L, T, M, or V;

5 T432 replaced with A, G, I, L, S, M, or V; V433 replaced with A, G, I, L, S, T, or M; T434 replaced with A, G, I, L, S, M, or V; G436 replaced with A, I, L, S, T, M, or V; Q437 replaced with N; G438 replaced with A, I, L, S, T, M, or V; L439 replaced with A, G, I, S, T, M, or V; R440 replaced with H, or K; Y441 replaced with F, or W; R442 replaced with H, or K; V443 replaced with A, G, I, L, S, T, or M; V444 replaced

10 with A, G, I, L, S, T, or M; L445 replaced with A, G, I, S, T, M, or V; I447 replaced with A, G, L, S, T, M, or V; D448 replaced with E; H449 replaced with K, or R; R450 replaced with H, or K; G451 replaced with A, I, L, S, T, M, or V; M452 replaced with A, G, I, L, S, T, or V; H453 replaced with K, or R; T454 replaced with A, G, I, L, S, M, or V; G455 replaced with A, I, L, S, T, M, or V; G456 replaced with A, I, L, S, T, M, or V; S458 replaced with A, G, I, L, T, M, or V; K460 replaced with H, or R;

15 T461 replaced with A, G, I, L, S, M, or V; K462 replaced with H, or R; H464 replaced with K, or R; I465 replaced with A, G, L, S, T, M, or V; K466 replaced with H, or R; E467 replaced with D; E468 replaced with D; I470 replaced with A, G, L, S, T, M, or V; V471 replaced with A, G, I, L, S, T, or M; T473 replaced with A, G, I, L, S, M, or

20 V; Y476 replaced with F, or W; K477 replaced with H, or R; K479 replaced with H, or R; E480 replaced with D; K481 replaced with H, or R; L482 replaced with A, G, I, S, T, M, or V; V484 replaced with A, G, I, L, S, T, or M; E485 replaced with D; A486 replaced with G, I, L, S, T, M, or V; K487 replaced with H, or R; L488 replaced with A, G, I, S, T, M, or V; W490 replaced with F, or Y; F491 replaced with W, or Y; K492

25 replaced with H, or R; Q493 replaced with N; A494 replaced with G, I, L, S, T, M, or V; Q495 replaced with N; E496 replaced with D; L497 replaced with A, G, I, S, T, M, or V; E498 replaced with D; E499 replaced with D; G500 replaced with A, I, L, S, T, M, or V; A501 replaced with G, I, L, S, T, M, or V; A502 replaced with G, I, L, S, T, M, or V; V503 replaced with A, G, I, L, S, T, or M; S504 replaced with A, G, I, L, T, M, or V; E505 replaced with D; E506 replaced with D; S508 replaced with A, G, I, L,

30 M, or V; F509 replaced with W, or Y; I510 replaced with A, G, L, S, T, M, or V; K512 replaced with H, or R; A513 replaced with G, I, L, S, T, M, or V; W514

replaced with F, or Y; S515 replaced with A, G, I, L, T, M, or V; A516 replaced with G, I, L, S, T, M, or V; T518 replaced with A, G, I, L, S, M, or V; V519 replaced with A, G, I, L, S, T, or M; T520 replaced with A, G, I, L, S, M, or V; G522 replaced with A, I, L, S, T, M, or V; V523 replaced with A, G, I, L, S, T, or M; G524 replaced with A, I, L, S, T, M, or V; T525 replaced with A, G, I, L, S, M, or V; Q526 replaced with N; V527 replaced with A, G, I, L, S, T, or M; R528 replaced with H, or K; I529 replaced with A, G, L, S, T, M, or V; V530 replaced with A, G, I, L, S, T, or M; R531 replaced with H, or K; Q533 replaced with N; V534 replaced with A, G, I, L, S, T, or M; L535 replaced with A, G, I, S, T, M, or V; L536 replaced with A, G, I, S, T, M, or V; S537 replaced with A, G, I, L, T, M, or V; F538 replaced with W, or Y; S539 replaced with A, G, I, L, T, M, or V; Q540 replaced with N; S541 replaced with A, G, I, L, T, M, or V; V542 replaced with A, G, I, L, S, T, or M; A543 replaced with G, I, L, S, T, M, or V; D544 replaced with E; L545 replaced with A, G, I, S, T, M, or V; I547 replaced with A, G, L, S, T, M, or V; D548 replaced with E; E549 replaced with D; E551 replaced with D; G552 replaced with A, I, L, S, T, M, or V; K554 replaced with H, or R; A556 replaced with G, I, L, S, T, M, or V; S557 replaced with A, G, I, L, T, M, or V; Q558 replaced with N; R559 replaced with H, or K; A560 replaced with G, I, L, S, T, M, or V; Y562 replaced with F, or W; A563 replaced with G, I, L, S, T, M, or V; G564 replaced with A, I, L, S, T, M, or V; S567 replaced with A, G, I, L, T, M, or V; G568 replaced with A, I, L, S, T, M, or V; E569 replaced with D; I570 replaced with A, G, L, S, T, M, or V; E572 replaced with D; F573 replaced with W, or Y; N574 replaced with Q; D576 replaced with E; E577 replaced with D; T578 replaced with A, G, I, L, S, M, or V; D579 replaced with E; G580 replaced with A, I, L, S, T, M, or V; L581 replaced with A, G, I, S, T, M, or V; F582 replaced with W, or Y; G583 replaced with A, I, L, S, T, M, or V; G584 replaced with A, I, L, S, T, M, or V; L585 replaced with A, G, I, S, T, M, or V; Q586 replaced with N; D587 replaced with E; F588 replaced with W, or Y; D589 replaced with E; E590 replaced with D; L591 replaced with A, G, I, S, T, M, or V; Y592 replaced with F, or W; D593 replaced with E; W594 replaced with F, or Y; E595 replaced with D; Y596 replaced with F, or W; E597 replaced with D; G598 replaced with A, I, L, S, T, M, or V; F599 replaced with W, or Y; T600 replaced with A, G, I, L, S, M, or V; K601 replaced with H, or R; S603 replaced with A, G, I, L, T, M, or V; E604 replaced with D; S605

replaced with A, G, I, L, T, M, or V; G607 replaced with A, I, L, S, T, M, or V; G608
 replaced with A, I, L, S, T, M, or V; G609 replaced with A, I, L, S, T, M, or V; V610
 replaced with A, G, I, L, S, T, or M; Q611 replaced with N; E612 replaced with D;
 A613 replaced with G, I, L, S, T, M, or V; V614 replaced with A, G, I, L, S, T, or M;
 5 V615 replaced with A, G, I, L, S, T, or M; S616 replaced with A, G, I, L, T, M, or V;
 L618 replaced with A, G, I, S, T, M, or V; N619 replaced with Q; K620 replaced with
 H, or R; Q621 replaced with N; T622 replaced with A, G, I, L, S, M, or V; R623
 replaced with H, or K; E624 replaced with D; A626 replaced with G, I, L, S, T, M, or
 V; E627 replaced with D; E628 replaced with D; N629 replaced with Q; L630
 10 replaced with A, G, I, S, T, M, or V; V632 replaced with A, G, I, L, S, T, or M; T633
 replaced with A, G, I, L, S, M, or V; S634 replaced with A, G, I, L, T, M, or V; R635
 replaced with H, or K; R636 replaced with H, or K; Q639 replaced with N; L640
 replaced with A, G, I, S, T, M, or V; L641 replaced with A, G, I, S, T, M, or V; K642
 replaced with H, or R; S643 replaced with A, G, I, L, T, M, or V; N645 replaced with
 15 Q; L646 replaced with A, G, I, S, T, M, or V; D647 replaced with E; A651 replaced
 with G, I, L, S, T, M, or V; R652 replaced with H, or K; W653 replaced with F, or Y;
 E654 replaced with D; I655 replaced with A, G, L, S, T, M, or V; G656 replaced with
 A, I, L, S, T, M, or V; K657 replaced with H, or R; W658 replaced with F, or Y;
 S659 replaced with A, G, I, L, T, M, or V; S662 replaced with A, G, I, L, T, M, or V;
 20 L663 replaced with A, G, I, S, T, M, or V; T664 replaced with A, G, I, L, S, M, or V;
 G666 replaced with A, I, L, S, T, M, or V; V667 replaced with A, G, I, L, S, T, or M;
 G668 replaced with A, I, L, S, T, M, or V; L669 replaced with A, G, I, S, T, M, or V;
 Q670 replaced with N; T671 replaced with A, G, I, L, S, M, or V; R672 replaced with
 H, or K; D673 replaced with E; V674 replaced with A, G, I, L, S, T, or M; F675
 25 replaced with W, or Y; S677 replaced with A, G, I, L, T, M, or V; H678 replaced with
 K, or R; L679 replaced with A, G, I, S, T, M, or V; L680 replaced with A, G, I, S, T,
 M, or V; S681 replaced with A, G, I, L, T, M, or V; R682 replaced with H, or K;
 E683 replaced with D; M684 replaced with A, G, I, L, S, T, or V; N685 replaced with
 Q; E686 replaced with D; T687 replaced with A, G, I, L, S, M, or V; V688 replaced
 30 with A, G, I, L, S, T, or M; I689 replaced with A, G, L, S, T, M, or V; L690 replaced
 with A, G, I, S, T, M, or V; A691 replaced with G, I, L, S, T, M, or V; D692 replaced
 with E; E693 replaced with D; L694 replaced with A, G, I, S, T, M, or V;

R696replaced with H, or K; Q697 replaced with N; K699 replaced with H, or R;
 S701replaced with A, G, I, L, T, M, or V; T702 replaced with A, G, I, L, S, M, or V;
 V703replaced with A, G, I, L, S, T, or M; Q704 replaced with N; A705 replaced with
 G, I,L, S, T, M, or V; N707 replaced with Q; R708 replaced with H, or K; F709
 5 replaced with W, or Y; N710 replaced with Q; A714 replaced with G, I, L, S, T, M, or
 V;W715 replaced with F, or Y; Y716 replaced with F, or W; A718 replaced with G,
 I,L, S, T, M, or V; Q719 replaced with N; W720 replaced with F, or Y; Q721 replaced
 with N; S724 replaced with A, G, I, L, T, M, or V; R725 replaced with H, or K;T726
 replaced with A, G, I, L, S, M, or V; G728 replaced with A, I, L, S, T, M, or V;G729
 10 replaced with A, I, L, S, T, M, or V; G730 replaced with A, I, L, S, T, M, or V;V731
 replaced with A, G, I, L, S, T, or M; Q732 replaced with N; K733 replaced with H, or
 R; R734 replaced with H, or K; E735 replaced with D; V736 replaced with A, G, I, L,
 S, T, or M; L737 replaced with A, G, I, S, T, M, or V; K739 replaced with H, or R;
 Q740 replaced with N; R741 replaced with H, or K; M742 replaced with A, G, I, L, S,
 15 T, or V; A743 replaced with G, I, L, S, T, M, or V; D744 replaced with E; G745
 replaced with A, I, L, S, T, M, or V; S746 replaced with A, G, I, L, T,M, or V; F747
 replaced with W, or Y; L748 replaced with A, G, I, S, T, M, or V;E749 replaced with
 D; L750 replaced with A, G, I, S, T, M, or V; E752 replaced withD; T753 replaced
 with A, G, I, L, S, M, or V; F754 replaced with W, or Y; S756replaced with A, G, I,
 20 L, T, M, or V; A757 replaced with G, I, L, S, T, M, or V; S758replaced with A, G, I,
 L, T, M, or V; K759 replaced with H, or R; A761 replaced with G, I, L, S, T, M, or V;
 Q763 replaced with N; Q764 replaced with N; A765replaced with G, I, L, S, T, M, or
 V; K767 replaced with H, or R; K768 replaced with H, or R; D769 replaced with E;
 D770 replaced with E; S773 replaced with A,G, I, L, T, M, or V; E774 replaced with
 25 D; W775 replaced with F, or Y; L776replaced with A, G, I, S, T, M, or V; L777
 replaced with A, G, I, S, T, M, or V; S778replaced with A, G, I, L, T, M, or V; D779
 replaced with E; W780 replaced with F,or Y; T781 replaced with A, G, I, L, S, M, or
 V; E782 replaced with D; S784replaced with A, G, I, L, T, M, or V; T785 replaced
 with A, G, I, L, S, M, or V; S786replaced with A, G, I, L, T, M, or V; G788 replaced
 30 with A, I, L, S, T, M, or V; E789replaced with D; G790 replaced with A, I, L, S, T,
 M, or V; T791 replaced with A, G,I, L, S, M, or V; Q792 replaced with N; T793
 replaced with A, G, I, L, S, M, or V;R794 replaced with H, or K; S795 replaced with

A, G, I, L, T, M, or V; A796 replaced with G, I, L, S, T, M, or V; I797 replaced with
 A, G, L, S, T, M, or V; R799 replaced with H, or K; K800 replaced with H, or R;
 M801 replaced with A, G, I, L, S, T, or V; L802 replaced with A, G, I, S, T, M, or V;
 K803 replaced with H, or R; T804 replaced with A, G, I, L, S, M, or V; G805 replaced
 5 with A, I, L, S, T, M, or V; L806 replaced with A, G, I, S, T, M, or V; S807 replaced
 with A, G, I, L, T, M, or V; T808 replaced with A, G, I, L, S, M, or V; V809 replaced
 with A, G, I, L, S, T, or M; V810 replaced with A, G, I, L, S, T, or M; N811 replaced
 with Q; S812 replaced with A, G, I, L, T, M, or V; T813 replaced with A, G, I, L, S,
 M, or V; L814 replaced with A, G, I, S, T, M, or V; L818 replaced with A, G, I, S, T,
 10 M, or V; F820 replaced with W, or Y; S821 replaced with A, G, I, L, T, M, or V;
 S822 replaced with A, G, I, L, T, M, or V; S823 replaced with A, G, I, L, T, M, or V;
 I824 replaced with A, G, L, S, T, M, or V; R825 replaced with H, or K; M828 replaced
 with A, G, I, L, S, T, or V; L829 replaced with A, G, I, S, T, M, or V; A830 replaced
 with G, I, L, S, T, M, or V; T831 replaced with A, G, I, L, S, M, or V; A833 replaced
 15 with G, I, L, S, T, M, or V; R834 replaced with H, or K; G836 replaced with A, I, L, S,
 T, M, or V; R837 replaced with H, or K; S839 replaced with A, G, I, L, T, M, or V;
 T840 replaced with A, G, I, L, S, M, or V; K841 replaced with H, or R; H842 replaced
 with K, or R; S843 replaced with A, G, I, L, T, M, or V; H845 replaced with K, or R;
 I846 replaced with A, G, L, S, T, M, or V; A847 replaced with G, I, L, S, T, M, or V;
 20 A848 replaced with G, I, L, S, T, M, or V; A849 replaced with G, I, L, S, T, M, or V;
 R850 replaced with H, or K; K851 replaced with H, or R; V852 replaced with A, G, I,
 L, S, T, or M; Y853 replaced with F, or W; I854 replaced with A, G, L, S, T, M, or
 V; Q855 replaced with N; T856 replaced with A, G, I, L, S, M, or V; R857 replaced
 with H, or K; R858 replaced with H, or K; Q859 replaced with N; R860 replaced with
 25 H, or K; K861 replaced with H, or R; L862 replaced with A, G, I, S, T, M, or V; H863
 replaced with K, or R; F864 replaced with W, or Y; V865 replaced with A, G, I, L, S,
 T, or M; V866 replaced with A, G, I, L, S, T, or M; G867 replaced with A, I, L, S, T,
 M, or V; G868 replaced with A, I, L, S, T, M, or V; F869 replaced with W, or Y; A870
 replaced with G, I, L, S, T, M, or V; Y871 replaced with F, or W; L872 replaced with
 30 A, G, I, S, T, M, or V; L873 replaced with A, G, I, S, T, M, or V; K875 replaced with
 H, or R; T876 replaced with A, G, I, L, S, M, or V; A877 replaced with G, I, L, S, T,
 M, or V; V878 replaced with A, G, I, L, S, T, or M; V879 replaced with A, G, I, L, S,

T, or M; L880 replaced with A, G, I, S, T, M, or V; R881 replaced with H, or K; A884
 replaced with G, I, L, S, T, M, or V; R885 replaced with H, or K; R886 replaced with
 H, or K; V887 replaced with A, G, I, L, S, T, or M; R888 replaced with H, or K; K889
 replaced with H, or R; L891 replaced with A, G, I, S, T, M, or V; I892 replaced with
 5 A, G, L, S, T, M, or V; T893 replaced with A, G, I, L, S, M, or V; W894 replaced with
 F, or Y; E895 replaced with D; K896 replaced with H, or R; D897 replaced with E;
 G898 replaced with A, I, L, S, T, M, or V; Q899 replaced with N; H900 replaced with
 K, or R; L901 replaced with A, G, I, S, T, M, or V; I902 replaced with A, G, L, S, T,
 M, or V; S903 replaced with A, G, I, L, T, M, or V; S904 replaced with A, G, I, L, T,
 10 M, or V; T905 replaced with A, G, I, L, S, M, or V; H906 replaced with K, or R; V907
 replaced with A, G, I, L, S, T, or M; T908 replaced with A, G, I, L, S, M, or V; V909
 replaced with A, G, I, L, S, T, or M; A910 replaced with G, I, L, S, T, M, or V; F912
 replaced with W, or Y; G913 replaced with A, I, L, S, T, M, or V; Y914 replaced with
 F, or W; L915 replaced with A, G, I, S, T, M, or V; K916 replaced with H, or R; I917
 15 replaced with A, G, L, S, T, M, or V; H918 replaced with K, or R; R919 replaced with
 H, or K; L920 replaced with A, G, I, S, T, M, or V; K921 replaced with H, or R; S923
 replaced with A, G, I, L, T, M, or V; D924 replaced with E; A925 replaced with G, I,
 L, S, T, M, or V; G926 replaced with A, I, L, S, T, M, or V; V927 replaced with A, G,
 I, L, S, T, or M; Y928 replaced with F, or W; T929 replaced with A, G, I, L, S, M, or
 20 V; S931 replaced with A, G, I, L, T, M, or V; A932 replaced with G, I, L, S, T, M, or
 V; G933 replaced with A, I, L, S, T, M, or V; A935 replaced with G, I, L, S, T, M, or
 V; R936 replaced with H, or K; E937 replaced with D; H938 replaced with K, or R;
 F939 replaced with W, or Y; V940 replaced with A, G, I, L, S, T, or M; I941 replaced
 with A, G, L, S, T, M, or V; K942 replaced with H, or R; L943 replaced with A, G, I,
 25 S, T, M, or V; I944 replaced with A, G, L, S, T, M, or V; G945 replaced with A, I, L,
 S, T, M, or V; G946 replaced with A, I, L, S, T, M, or V; N947 replaced with Q; R948
 replaced with H, or K; K949 replaced with H, or R; L950 replaced with A, G, I, S, T,
 M, or V; V951 replaced with A, G, I, L, S, T, or M; A952 replaced with G, I, L, S, T,
 M, or V; R953 replaced with H, or K; L955 replaced with A, G, I, S, T, M, or V; S956
 30 replaced with A, G, I, L, T, M, or V; R958 replaced with H, or K; S959 replaced with
 A, G, I, L, T, M, or V; E960 replaced with D; E961 replaced with D; E962 replaced
 with D; V963 replaced with A, G, I, L, S, T, or M; L964 replaced with A, G, I, S, T,

M, or V; A965 replaced with G, I, L, S, T, M, or V; G966 replaced with A, I, L, S, T, M, or V; R967 replaced with H, or K; K968 replaced with H, or R; G969 replaced with A, I, L, S, T, M, or V; G970 replaced with A, I, L, S, T, M, or V; K972 replaced with H, or R; E973 replaced with D; A974 replaced with G, I, L, S, T, M, or V; L975
 5 replaced with A, G, I, S, T, M, or V; Q976 replaced with N; T977 replaced with A, G, I, L, S, M, or V; H978 replaced with K, or R; K979 replaced with H, or R; H980 replaced with K, or R; Q981 replaced with N; N982 replaced with Q; G983 replaced with A, I, L, S, T, M, or V; I984 replaced with A, G, L, S, T, M, or V; F985 replaced with W, or Y; S986 replaced with A, G, I, L, T, M, or V; N987 replaced with Q; G988
 10 replaced with A, I, L, S, T, M, or V; S989 replaced with A, G, I, L, T, M, or V; K990 replaced with H, or R; A991 replaced with G, I, L, S, T, M, or V; E992 replaced with D; K993 replaced with H, or R; R994 replaced with H, or K; G995 replaced with A, I, L, S, T, M, or V; L996 replaced with A, G, I, S, T, M, or V; A997 replaced with G, I, L, S, T, M, or V; A998 replaced with G, I, L, S, T, M, or V; N999 replaced with
 15 Q; G1001 replaced with A, I, L, S, T, M, or V; S1002 replaced with A, G, I, L, T, M, or V; R1003 replaced with H, or K; Y1004 replaced with F, or W; D1005 replaced with E; D1006 replaced with E; L1007 replaced with A, G, I, S, T, M, or V; V1008 replaced with A, G, I, L, S, T, or M; S1009 replaced with A, G, I, L, T, M, or V; R1010 replaced with H, or K; L1011 replaced with A, G, I, S, T, M, or V;
 20 L1012 replaced with A, G, I, S, T, M, or V; E1013 replaced with D; Q1014 replaced with N; G1015 replaced with A, I, L, S, T, M, or V; G1016 replaced with A, I, L, S, T, M, or V; W1017 replaced with F, or Y; G1019 replaced with A, I, L, S, T, M, or V; E1020 replaced with D; L1021 replaced with A, G, I, S, T, M, or V; L1022 replaced with A, G, I, S, T, M, or V; A1023 replaced with G, I, L, S, T, M, or V;
 25 S1024 replaced with A, G, I, L, T, M, or V; W1025 replaced with F, or Y; E1026 replaced with D; A1027 replaced with G, I, L, S, T, M, or V; Q1028 replaced with N; D1029 replaced with E; S1030 replaced with A, G, I, L, T, M, or V; A1031 replaced with G, I, L, S, T, M, or V; E1032 replaced with D; R1033 replaced with H, or K; N1034 replaced with Q; T1035 replaced with A, G, I, L, S, M, or V; T1036 replaced
 30 with A, G, I, L, S, M, or V; S1037 replaced with A, G, I, L, T, M, or V; E1038 replaced with D; E1039 replaced with D; D1040 replaced with E; G1042 replaced with A, I, L, S, T, M, or V; A1043 replaced with G, I, L, S, T, M, or V; E1044 replaced

with D; Q1045 replaced with N; V1046 replaced with A, G, I, L, S, T, or M; L1047
 replaced with A, G, I, S, T, M, or V; L1048 replaced with A, G, I, S, T, M, or V;
 H1049 replaced with K, or R; L1050 replaced with A, G, I, S, T, M, or V; F1052
 replaced with W, or Y; T1053 replaced with A, G, I, L, S, M, or V; M1054 replaced
 5 with A, G, I, L, S, T, or V; V1055 replaced with A, G, I, L, S, T, or M; T1056 replaced
 with A, G, I, L, S, M, or V; E1057 replaced with D; Q1058 replaced with N;
 R1059 replaced with H, or K; R1060 replaced with H, or K; L1061 replaced with A,
 G, I, S, T, M, or V; D1062 replaced with E; D1063 replaced with E; I1064 replaced
 with A, G, L, S, T, M, or V; L1065 replaced with A, G, I, S, T, M, or V; G1066
 10 replaced with A, I, L, S, T, M, or V; N1067 replaced with Q; L1068 replaced with A,
 G, I, S, T, M, or V; S1069 replaced with A, G, I, L, T, M, or V; Q1070 replaced with
 N; Q1071 replaced with N; E1073 replaced with D; E1074 replaced with D; L1075
 replaced with A, G, I, S, T, M, or V; R1076 replaced with H, or K; D1077 replaced
 with E; L1078 replaced with A, G, I, S, T, M, or V; Y1079 replaced with F, or W;
 15 S1080 replaced with A, G, I, L, T, M, or V; K1081 replaced with H, or R; H1082
 replaced with K, or R; L1083 replaced with A, G, I, S, T, M, or V; V1084 replaced
 with A, G, I, L, S, T, or M; A1085 replaced with G, I, L, S, T, M, or V; Q1086
 replaced with N; L1087 replaced with A, G, I, S, T, M, or V; A1088 replaced with G,
 I, L, S, T, M, or V; Q1089 replaced with N; E1090 replaced with D; I1091 replaced
 20 with A, G, L, S, T, M, or V; F1092 replaced with W, or Y; R1093 replaced with H, or
 K; S1094 replaced with A, G, I, L, T, M, or V; H1095 replaced with K, or R; L1096
 replaced with A, G, I, S, T, M, or V; E1097 replaced with D; H1098 replaced with K,
 or R; Q1099 replaced with N; D1100 replaced with E; T1101 replaced with A, G, I, L,
 S, M, or V; L1102 replaced with A, G, I, S, T, M, or V; L1103 replaced with A, G, I,
 25 S, T, M, or V; K1104 replaced with H, or R; S1106 replaced with A, G, I, L, T, M,
 or V; E1107 replaced with D; R1108 replaced with H, or K; R1109 replaced with H,
 or K; T1110 replaced with A, G, I, L, S, M, or V; S1111 replaced with A, G, I, L, T,
 M, or V; V1113 replaced with A, G, I, L, S, T, or M; T1114 replaced with A, G, I, L,
 S, M, or V; L1115 replaced with A, G, I, S, T, M, or V; S1116 replaced with A, G, I,
 30 L, T, M, or V; H1118 replaced with K, or R; K1119 replaced with H, or R;
 H1120 replaced with K, or R; V1121 replaced with A, G, I, L, S, T, or M; S1122
 replaced with A, G, I, L, T, M, or V; G1123 replaced with A, I, L, S, T, M, or V;

- F1124replaced with W, or Y; S1125 replaced with A, G, I, L, T, M, or V; S1126 replaced with A, G, I, L, T, M, or V; S1127 replaced with A, G, I, L, T, M, or V; L1128replaced with A, G, I, S, T, M, or V; R1129 replaced with H, or K; T1130 replaced with A, G, I, L, S, M, or V; S1131 replaced with A, G, I, L, T, M, or V;
- 5 S1132replaced with A, G, I, L, T, M, or V; T1133 replaced with A, G, I, L, S, M, or V;G1134 replaced with A, I, L, S, T, M, or V; D1135 replaced with E; A1136 replaced with G, I, L, S, T, M, or V; G1137 replaced with A, I, L, S, T, M, or V; G1138replaced with A, I, L, S, T, M, or V; G1139 replaced with A, I, L, S, T, M, or V;S1140 replaced with A, G, I, L, T, M, or V; R1141 replaced with H, or K;
- 10 R1142replaced with H, or K; H1144 replaced with K, or R; R1145 replaced with H, or K;K1146 replaced with H, or R; T1148 replaced with A, G, I, L, S, M, or V; I1149replaced with A, G, L, S, T, M, or V; L1150 replaced with A, G, I, S, T, M, or V;R1151 replaced with H, or K; K1152 replaced with H, or R; I1153 replaced with A,G, L, S, T, M, or V; S1154 replaced with A, G, I, L, T, M, or V; A1155 replaced
- 15 withG, I, L, S, T, M, or V; A1156 replaced with G, I, L, S, T, M, or V; Q1157 replaced with N; Q1158 replaced with N; L1159 replaced with A, G, I, S, T, M, or V; S1160replaced with A, G, I, L, T, M, or V; A1161 replaced with G, I, L, S, T, M, or V;S1162 replaced with A, G, I, L, T, M, or V; E1163 replaced with D; V1164 replaced with A, G, I, L, S, T, or M; V1165 replaced with A, G, I, L, S, T, or M;
- 20 T1166replaced with A, G, I, L, S, M, or V; H1167 replaced with K, or R; L1168 replaced with A, G, I, S, T, M, or V; G1169 replaced with A, I, L, S, T, M, or V; Q1170replaced with N; T1171 replaced with A, G, I, L, S, M, or V; V1172 replaced with A,G, I, L, S, T, or M; A1173 replaced with G, I, L, S, T, M, or V; L1174 replaced withA, G, I, S, T, M, or V; A1175 replaced with G, I, L, S, T, M, or V;
- 25 S1176 replaced with A, G, I, L, T, M, or V; G1177 replaced with A, I, L, S, T, M, or V; T1178replaced with A, G, I, L, S, M, or V; L1179 replaced with A, G, I, S, T, M, or V;S1180 replaced with A, G, I, L, T, M, or V; V1181 replaced with A, G, I, L, S, T, orM; L1182 replaced with A, G, I, S, T, M, or V; L1183 replaced with A, G, I, S, T, M,or V; H1184 replaced with K, or R; E1186 replaced with D; A1187 replaced
- 30 with G,I, L, S, T, M, or V; I1188 replaced with A, G, L, S, T, M, or V; G1189 replaced withA, I, L, S, T, M, or V; H1190 replaced with K, or R; R1192 replaced with H, or K;T1194 replaced with A, G, I, L, S, M, or V; I1195 replaced with A, G, L,

S, T, M, or V; S1196 replaced with A, G, I, L, T, M, or V; W1197 replaced with F, or Y; A1198 replaced with G, I, L, S, T, M, or V; R1199 replaced with H, or K; N1200 replaced with Q; G1201 replaced with A, I, L, S, T, M, or V; E1202 replaced with D; E1203 replaced with D; V1204 replaced with A, G, I, L, S, T, or M; Q1205 replaced
5 with N; F1206 replaced with W, or Y; S1207 replaced with A, G, I, L, T, M, or V; D1208 replaced with E; R1209 replaced with H, or K; I1210 replaced with A, G, L, S, T, M, or V; L1211 replaced with A, G, I, S, T, M, or V; L1212 replaced with A, G, I, S, T, M, or V; Q1213 replaced with N; D1215 replaced with E; D1216 replaced with E; S1217 replaced with A, G, I, L, T, M, or V; L1218 replaced with A, G, I, S, T, M,
10 or V; Q1219 replaced with N; I1220 replaced with A, G, L, S, T, M, or V; L1221 replaced with A, G, I, S, T, M, or V; A1222 replaced with G, I, L, S, T, M, or V; V1224 replaced with A, G, I, L, S, T, or M; E1225 replaced with D; A1226 replaced with G, I, L, S, T, M, or V; D1227 replaced with E; V1228 replaced with A, G, I, L, S, T, or M; G1229 replaced with A, I, L, S, T, M, or V; F1230 replaced with
15 W, or Y; Y1231 replaced with F, or W; T1232 replaced with A, G, I, L, S, M, or V; N1234 replaced with Q; A1235 replaced with G, I, L, S, T, M, or V; T1236 replaced with A, G, I, L, S, M, or V; N1237 replaced with Q; A1238 replaced with G, I, L, S, T, M, or V; L1239 replaced with A, G, I, S, T, M, or V; G1240 replaced with A, I, L, S, T, M, or V; Y1241 replaced with F, or W; D1242 replaced with E; S1243 replaced
20 with A, G, I, L, T, M, or V; V1244 replaced with A, G, I, L, S, T, or M; S1245 replaced with A, G, I, L, T, M, or V; I1246 replaced with A, G, L, S, T, M, or V; A1247 replaced with G, I, L, S, T, M, or V; V1248 replaced with A, G, I, L, S, T, or M; T1249 replaced with A, G, I, L, S, M, or V; L1250 replaced with A, G, I, S, T, M, or V; A1251 replaced with G, I, L, S, T, M, or V; G1252 replaced with A, I, L, S, T,
25 M, or V; K1253 replaced with H, or R; L1255 replaced with A, G, I, S, T, M, or V; V1256 replaced with A, G, I, L, S, T, or M; K1257 replaced with H, or R; T1258 replaced with A, G, I, L, S, M, or V; S1259 replaced with A, G, I, L, T, M, or V; R1260 replaced with H, or K; M1261 replaced with A, G, I, L, S, T, or V; T1262 replaced with A, G, I, L, S, M, or V; V1263 replaced with A, G, I, L, S, T, or M;
30 I1264 replaced with A, G, L, S, T, M, or V; N1265 replaced with Q; T1266 replaced with A, G, I, L, S, M, or V; E1267 replaced with D; K1268 replaced with H, or R; A1270 replaced with G, I, L, S, T, M, or V; V1271 replaced with A, G, I, L, S, T, or

M;T1272 replaced with A, G, I, L, S, M, or V; V1273 replaced with A, G, I, L, S, T,
 orM; D1274 replaced with E; I1275 replaced with A, G, L, S, T, M, or V;
 G1276replaced with A, I, L, S, T, M, or V; S1277 replaced with A, G, I, L, T, M, or
 V;T1278 replaced with A, G, I, L, S, M, or V; I1279 replaced with A, G, L, S, T, M,
 5 orV; K1280 replaced with H, or R; T1281 replaced with A, G, I, L, S, M, or V;
 V1282replaced with A, G, I, L, S, T, or M; Q1283 replaced with N; G1284 replaced
 with A,I, L, S, T, M, or V; V1285 replaced with A, G, I, L, S, T, or M; N1286
 replaced withQ; V1287 replaced with A, G, I, L, S, T, or M; T1288 replaced with A,
 G, I, L, S, M,or V; I1289 replaced with A, G, L, S, T, M, or V; N1290 replaced with
 10 Q; Q1292replaced with N; V1293 replaced with A, G, I, L, S, T, or M; A1294
 replaced with G,I, L, S, T, M, or V; G1295 replaced with A, I, L, S, T, M, or V;
 V1296 replaced withA, G, I, L, S, T, or M; E1298 replaced with D; A1299 replaced
 with G, I, L, S, T, M,or V; E1300 replaced with D; V1301 replaced with A, G, I, L, S,
 T, or M; T1302replaced with A, G, I, L, S, M, or V; W1303 replaced with F, or Y;
 15 F1304 replaced with W, or Y; R1305 replaced with H, or K; N1306 replaced with Q;
 K1307replaced with H, or R; S1308 replaced with A, G, I, L, T, M, or V; K1309
 replaced with H, or R; L1310 replaced with A, G, I, S, T, M, or V; G1311 replaced
 with A, I,L, S, T, M, or V; S1312 replaced with A, G, I, L, T, M, or V; H1314
 replaced with K,or R; H1315 replaced with K, or R; L1316 replaced with A, G, I, S,
 20 T, M, or V;H1317 replaced with K, or R; E1318 replaced with D; G1319 replaced
 with A, I, L,S, T, M, or V; S1320 replaced with A, G, I, L, T, M, or V; L1321
 replaced with A, G,I, S, T, M, or V; L1322 replaced with A, G, I, S, T, M, or V;
 L1323 replaced with A,G, I, S, T, M, or V; T1324 replaced with A, G, I, L, S, M, or
 V; N1325 replaced withQ; V1326 replaced with A, G, I, L, S, T, or M; S1327
 25 replaced with A, G, I, L, T, M,or V; S1328 replaced with A, G, I, L, T, M, or V;
 S1329 replaced with A, G, I, L, T,M, or V; D1330 replaced with E; Q1331 replaced
 with N; G1332 replaced with A, I,L, S, T, M, or V; L1333 replaced with A, G, I, S, T,
 M, or V; Y1334 replaced with F,or W; S1335 replaced with A, G, I, L, T, M, or V;
 R1337 replaced with H, or K;A1338 replaced with G, I, L, S, T, M, or V; A1339
 30 replaced with G, I, L, S, T, M, orV; N1340 replaced with Q; L1341 replaced with A,
 G, I, S, T, M, or V; H1342replaced with K, or R; G1343 replaced with A, I, L, S, T,
 M, or V; E1344 replaced with D; L1345 replaced with A, G, I, S, T, M, or V; T1346

replaced with A, G, I, L, S, M, or V; E1347 replaced with D; S1348 replaced with A, G, I, L, T, M, or V; T1349 replaced with A, G, I, L, S, M, or V; Q1350 replaced with N; L1351 replaced with A, G, I, S, T, M, or V; L1352 replaced with A, G, I, S, T, M, or V; I1353 replaced with A, G, L, S, T, M, or V; L1354 replaced with A, G, I, S, T, M, or V; D1355 replaced with E; Q1358 replaced with N; V1359 replaced with A, G, I, L, S, T, or M; T1361 replaced with A, G, I, L, S, M, or V; Q1362 replaced with N; L1363 replaced with A, G, I, S, T, M, or V; E1364 replaced with D; D1365 replaced with E; I1366 replaced with A, G, L, S, T, M, or V; R1367 replaced with H, or K; A1368 replaced with G, I, L, S, T, M, or V; L1369 replaced with A, G, I, S, T, M, or V; L1370 replaced with A, G, I, S, T, M, or V; A1371 replaced with G, I, L, S, T, M, or V; A1372 replaced with G, I, L, S, T, M, or V; T1373 replaced with A, G, I, L, S, M, or V; G1374 replaced with A, I, L, S, T, M, or V; N1376 replaced with Q; L1377 replaced with A, G, I, S, T, M, or V; S1379 replaced with A, G, I, L, T, M, or V; V1380 replaced with A, G, I, L, S, T, or M; L1381 replaced with A, G, I, S, T, M, or V; T1382 replaced with A, G, I, L, S, M, or V; S1383 replaced with A, G, I, L, T, M, or V; L1385 replaced with A, G, I, S, T, M, or V; G1386 replaced with A, I, L, S, T, M, or V; T1387 replaced with A, G, I, L, S, M, or V; Q1388 replaced with N; L1389 replaced with A, G, I, S, T, M, or V; V1390 replaced with A, G, I, L, S, T, or M; L1391 replaced with A, G, I, S, T, M, or V; D1392 replaced with E; G1394 replaced with A, I, L, S, T, M, or V; N1395 replaced with Q; S1396 replaced with A, G, I, L, T, M, or V; A1397 replaced with G, I, L, S, T, M, or V; L1398 replaced with A, G, I, S, T, M, or V; L1399 replaced with A, G, I, S, T, M, or V; G1400 replaced with A, I, L, S, T, M, or V; I1403 replaced with A, G, L, S, T, M, or V; K1404 replaced with H, or R; G1405 replaced with A, I, L, S, T, M, or V; H1406 replaced with K, or R; V1408 replaced with A, G, I, L, S, T, or M; N1410 replaced with Q; I1411 replaced with A, G, L, S, T, M, or V; T1412 replaced with A, G, I, L, S, M, or V; W1413 replaced with F, or Y; F1414 replaced with W, or Y; H1415 replaced with K, or R; G1416 replaced with A, I, L, S, T, M, or V; G1417 replaced with A, I, L, S, T, M, or V; Q1418 replaced with N; I1420 replaced with A, G, L, S, T, M, or V; V1421 replaced with A, G, I, L, S, T, or M; T1422 replaced with A, G, I, L, S, M, or V; A1423 replaced with G, I, L, S, T, M, or V; T1424 replaced with A, G, I, L, S, M, or V; G1425 replaced with A, I, L, S, T, M, or V; L1426 replaced with A, G, I, S, T,

M, or V; T1427 replaced with A, G, I, L, S, M, or V; H1428 replaced with K, or
 R; H1429 replaced with K, or R; I1430 replaced with A, G, L, S, T, M, or V;
 L1431 replaced with A, G, I, S, T, M, or V; A1432 replaced with G, I, L, S, T, M, or
 V; A1433 replaced with G, I, L, S, T, M, or V; G1434 replaced with A, I, L, S, T, M,
 5 or V; Q1435 replaced with N; I1436 replaced with A, G, L, S, T, M, or V;
 L1437 replaced with A, G, I, S, T, M, or V; Q1438 replaced with N; V1439 replaced
 with A, G, I, L, S, T, or M; A1440 replaced with G, I, L, S, T, M, or V; N1441
 replaced with Q; L1442 replaced with A, G, I, S, T, M, or V; S1443 replaced with A,
 G, I, L, T, M, or V; G1444 replaced with A, I, L, S, T, M, or V; G1445 replaced with
 10 A, I, L, S, T, M, or V; S1446 replaced with A, G, I, L, T, M, or V; Q1447 replaced
 with N; G1448 replaced with A, I, L, S, T, M, or V; E1449 replaced with D; F1450
 replaced with W, or Y; S1451 replaced with A, G, I, L, T, M, or V; L1453 replaced
 with A, G, I, S, T, M, or V; A1454 replaced with G, I, L, S, T, M, or V; Q1455
 replaced with N; N1456 replaced with Q; E1457 replaced with D; A1458 replaced
 15 with G, I, L, S, T, M, or V; G1459 replaced with A, I, L, S, T, M, or V; V1460
 replaced with A, G, I, L, S, T, or M; L1461 replaced with A, G, I, S, T, M, or V;
 M1462 replaced with A, G, I, L, S, T, or V; Q1463 replaced with N; K1464 replaced
 with H, or R; A1465 replaced with G, I, L, S, T, M, or V; S1466 replaced with A, G, I,
 L, T, M, or V; L1467 replaced with A, G, I, S, T, M, or V; V1468 replaced with A, G,
 20 I, L, S, T, or M; I1469 replaced with A, G, L, S, T, M, or V; Q1470 replaced with N;
 D1471 replaced with E; Y1472 replaced with F, or W; W1473 replaced with F, or Y;
 W1474 replaced with F, or Y; S1475 replaced with A, G, I, L, T, M, or V; V1476
 replaced with A, G, I, L, S, T, or M; D1477 replaced with E; R1478 replaced with H,
 or K; L1479 replaced with A, G, I, S, T, M, or V; A1480 replaced with G, I, L, S, T,
 25 M, or V; T1481 replaced with A, G, I, L, S, M, or V; S1483 replaced with A, G, I, L,
 T, M, or V; A1484 replaced with G, I, L, S, T, M, or V; S1485 replaced with A, G, I,
 L, T, M, or V; G1487 replaced with A, I, L, S, T, M, or V; N1488 replaced with Q;
 R1489 replaced with H, or K; G1490 replaced with A, I, L, S, T, M, or V; V1491
 replaced with A, G, I, L, S, T, or M; Q1492 replaced with N; Q1493 replaced with N;
 30 R1495 replaced with H, or K; L1496 replaced with A, G, I, S, T, M, or V; R1497
 replaced with H, or K; L1499 replaced with A, G, I, S, T, M, or V; L1500 replaced
 with A, G, I, S, T, M, or V; N1501 replaced with Q; S1502 replaced with A, G, I, L, T,

M, or V; T1503 replaced with A, G, I, L, S, M, or V; E1504 replaced with D; V1505 replaced with A, G, I, L, S, T, or M; N1506 replaced with Q; A1508 replaced with G, I, L, S, T, M, or V; H1509 replaced with K, or R; A1511 replaced with G, I, L, S, T, M, or V; G1512 replaced with A, I, L, S, T, M, or V; K1513 replaced with H, or R;

5 V1514 replaced with A, G, I, L, S, T, or M; R1515 replaced with H, or K; A1517 replaced with G, I, L, S, T, M, or V; V1518 replaced with A, G, I, L, S, T, or M; Q1519 replaced with N; I1521 replaced with A, G, L, S, T, M, or V; A1522 replaced with G, I, L, S, T, M, or V; N1524 replaced with Q; R1525 replaced with H, or K; R1526 replaced with H, or K; D1527 replaced with E; S1530 replaced with A, G, I, L,

10 T, M, or V; R1531 replaced with H, or K; W1532 replaced with F, or Y; M1533 replaced with A, G, I, L, S, T, or V; V1534 replaced with A, G, I, L, S, T, or M; T1535 replaced with A, G, I, L, S, M, or V; S1536 replaced with A, G, I, L, T, M, or V; W1537 replaced with F, or Y; S1538 replaced with A, G, I, L, T, M, or V; A1539 replaced with G, I, L, S, T, M, or V; T1541 replaced with A, G, I, L, S, M, or

15 V; R1542 replaced with H, or K; S1543 replaced with A, G, I, L, T, M, or V; G1545 replaced with A, I, L, S, T, M, or V; G1546 replaced with A, I, L, S, T, M, or V; G1547 replaced with A, I, L, S, T, M, or V; V1548 replaced with A, G, I, L, S, T, or M; Q1549 replaced with N; T1550 replaced with A, G, I, L, S, M, or V; R1551 replaced with H, or K; R1552 replaced with H, or K; V1553 replaced with A,

20 G, I, L, S, T, or M; T1554 replaced with A, G, I, L, S, M, or V; Q1556 replaced with N; K1557 replaced with H, or R; L1558 replaced with A, G, I, S, T, M, or V; K1559 replaced with H, or R; A1560 replaced with G, I, L, S, T, M, or V; S1561 replaced with A, G, I, L, T, M, or V; G1562 replaced with A, I, L, S, T, M, or V; I1563 replaced with A, G, L, S, T, M, or V; S1564 replaced with A, G, I, L, T, M, or

25 V; T1565 replaced with A, G, I, L, S, M, or V; V1567 replaced with A, G, I, L, S, T, or M; S1568 replaced with A, G, I, L, T, M, or V; N1569 replaced with Q; D1570 replaced with E; M1571 replaced with A, G, I, L, S, T, or V; T1573 replaced with A, G, I, L, S, M, or V; Q1574 replaced with N; V1575 replaced with A, G, I, L, S, T, or M; A1576 replaced with G, I, L, S, T, M, or V; K1577 replaced with H, or R;

30 R1578 replaced with H, or K; V1580 replaced with A, G, I, L, S, T, or M; D1581 replaced with E; T1582 replaced with A, G, I, L, S, M, or V; Q1583 replaced with N; A1584 replaced with G, I, L, S, T, M, or V; N1586 replaced with Q; Q1587 replaced

withN; Q1588 replaced with N; L1589 replaced with A, G, I, S, T, M, or V;
V1591replaced with A, G, I, L, S, T, or M; E1592 replaced with D; W1593 replaced
with F,or Y; A1594 replaced with G, I, L, S, T, M, or V; F1595 replaced with W, or
Y;S1596 replaced with A, G, I, L, T, M, or V; S1597 replaced with A, G, I, L, T, M,
5 orV; W1598 replaced with F, or Y; G1599 replaced with A, I, L, S, T, M, or V;
Q1600replaced with N; N1602 replaced with Q; G1603 replaced with A, I, L, S, T, M,
orV; I1606 replaced with A, G, L, S, T, M, or V; G1607 replaced with A, I, L, S, T,
M,or V; H1609 replaced with K, or R; L1610 replaced with A, G, I, S, T, M, or
V;A1611 replaced with G, I, L, S, T, M, or V; V1612 replaced with A, G, I, L, S, T,
10 orM; Q1613 replaced with N; H1614 replaced with K, or R; R1615 replaced with H,or
K; Q1616 replaced with N; V1617 replaced with A, G, I, L, S, T, or M;
F1618replaced with W, or Y; Q1620 replaced with N; T1621 replaced with A, G, I, L,
S,M, or V; R1622 replaced with H, or K; D1623 replaced with E; G1624 replaced
with A, I, L, S, T, M, or V; I1625 replaced with A, G, L, S, T, M, or V;
15 T1626replaced with A, G, I, L, S, M, or V; L1627 replaced with A, G, I, S, T, M, or
V;S1629 replaced with A, G, I, L, T, M, or V; E1630 replaced with D; Q1631
replaced with N; S1633 replaced with A, G, I, L, T, M, or V; A1634 replaced with G,
I, L, S,T, M, or V; L1635 replaced with A, G, I, S, T, M, or V; R1637 replaced with
H, orK; V1639 replaced with A, G, I, L, S, T, or M; S1640 replaced with A, G, I, L,
20 T, M,or V; T1641 replaced with A, G, I, L, S, M, or V; Q1642 replaced with N;
N1643replaced with Q; W1645 replaced with F, or Y; S1646 replaced with A, G, I, L,
T, M,or V; E1647 replaced with D; A1648 replaced with G, I, L, S, T, M, or V;
S1650replaced with A, G, I, L, T, M, or V; V1651 replaced with A, G, I, L, S, T, or
M;H1652 replaced with K, or R; W1653 replaced with F, or Y; R1654 replaced
25 withH, or K; V1655 replaced with A, G, I, L, S, T, or M; S1656 replaced with A, G, I,
L,T, M, or V; L1657 replaced with A, G, I, S, T, M, or V; W1658 replaced with F,
orY; T1659 replaced with A, G, I, L, S, M, or V; L1660 replaced with A, G, I, S, T,
M,or V; T1662 replaced with A, G, I, L, S, M, or V; A1663 replaced with G, I, L, S,
T,M, or V; T1664 replaced with A, G, I, L, S, M, or V; G1666 replaced with A, I, L,
30 S,T, M, or V; N1667 replaced with Q; Y1668 replaced with F, or W; G1669 replaced
with A, I, L, S, T, M, or V; F1670 replaced with W, or Y; Q1671 replaced with
N;S1672 replaced with A, G, I, L, T, M, or V; R1673 replaced with H, or K;

R1674replaced with H, or K; V1675 replaced with A, G, I, L, S, T, or M; E1676
 replaced with D; V1678 replaced with A, G, I, L, S, T, or M; H1679 replaced with K,
 or R;A1680 replaced with G, I, L, S, T, M, or V; R1681 replaced with H, or K;
 T1682replaced with A, G, I, L, S, M, or V; N1683 replaced with Q; K1684 replaced
 5 withH, or R; A1685 replaced with G, I, L, S, T, M, or V; V1686 replaced with A, G, I,
 L,S, T, or M; E1688 replaced with D; H1689 replaced with K, or R; L1690 replaced
 with A, G, I, S, T, M, or V; S1692 replaced with A, G, I, L, T, M, or V;
 W1693replaced with F, or Y; G1694 replaced with A, I, L, S, T, M, or V; R1696
 replaced with H, or K; A1698 replaced with G, I, L, S, T, M, or V; N1699 replaced
 10 with Q;W1700 replaced with F, or Y; Q1701 replaced with N; R1702 replaced with
 H, orK; N1704 replaced with Q; I1705 replaced with A, G, L, S, T, M, or V;
 T1706replaced with A, G, I, L, S, M, or V; E1709 replaced with D; N1710 replaced
 withQ; M1711 replaced with A, G, I, L, S, T, or V; E1712 replaced with D;
 R1714replaced with H, or K; D1715 replaced with E; T1716 replaced with A, G, I, L,
 15 S, M,or V; T1717 replaced with A, G, I, L, S, M, or V; R1718 replaced with H, or
 K;Y1719 replaced with F, or W; E1721 replaced with D; K1722 replaced with H, orR;
 V1723 replaced with A, G, I, L, S, T, or M; K1724 replaced with H, or R;
 Q1725replaced with N; L1726 replaced with A, G, I, S, T, M, or V; K1727 replaced
 with H,or R; L1728 replaced with A, G, I, S, T, M, or V; Q1730 replaced with N;
 20 L1731replaced with A, G, I, S, T, M, or V; S1732 replaced with A, G, I, L, T, M, or
 V;Q1733 replaced with N; F1734 replaced with W, or Y; K1735 replaced with H,
 orR; S1736 replaced with A, G, I, L, T, M, or V; R1737 replaced with H, or K;
 G1740replaced with A, I, L, S, T, M, or V; T1741 replaced with A, G, I, L, S, M, or
 V;G1743 replaced with A, I, L, S, T, M, or V; K1744 replaced with H, or R; or A1745
 25 replaced with G, I, L, S, T, M, or V.

The resulting constructs can be routinely screened for activities or functions
 described throughout the specification and known in the art. Preferably, the resulting
 constructs have an increased THRAP activity or function, while the remaining
 THRAP activities or functions are maintained. More preferably, the resulting
 30 constructs have more than one increased THRAP activity or function, while the
 remaining THRAP activities or functions are maintained.

Besides conservative amino acid substitution, non-conservative substitutions are also preferred. For example, preferred non-conservative substitutions of THRAP (SEQ ID NO:89) include: M1 replaced with D,E, H, K, R, N, Q, F, W, Y, P, or C; E2 replaced with H, K, R, A, G, I, L, S, T, M, V,N, Q, F, W, Y, P, or C; C3 replaced with

5 D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q,F, W, Y, or P; C4 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; R5 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R6 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A7 replaced with D,E, H, K, R, N, Q, F, W, Y, P, or C; T8 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P9 replaced with D, E, H, K, R, A, G, I, L,

10 S, T, M, V, N, Q, F, W, Y, or C; G10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T11 replaced with D, E, H, K, R,N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L14 replaced with D, E, H, K, R,N, Q, F, W, Y, P, or C; F15 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V,P, or C; L16 replaced with D, E, H, K, R, N, Q,

15 F, W, Y, P, or C; A17 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F18 replaced with D, E, H, K, R, N, Q, A, G, I,L, S, T, M, V, P, or C; L19 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L20 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L21 replaced with D, E, H, K, R,N, Q, F, W, Y, P, or C; S22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S23 replaced with D, E, H, K, R, N, Q, F, W, Y, P,

20 or C; R24 replaced with D, E, A, G, I,L, S, T, M, V, N, Q, F, W, Y, P, or C; T25 replaced with D, E, H, K, R, N, Q, F, W, Y,P, or C; A26 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R27 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S28 replaced with D, E, H, K, R,N, Q, F, W, Y, P, or C; E29 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W,Y, P, or C; E30 replaced with H, K, R, A, G,

25 I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D31 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R32 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D33 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G34 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; L35 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; W36 replaced with D, E, H, K, R, N, Q, A, G, I, L, S,

30 T, M, V, P, or C; D37 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A38 replaced with D, E,H, K, R, N, Q, F, W, Y, P, or C; W39 replaced with D, E, H, K, R, N, Q, A, G, I, L, S,T, M, V, P, or C; G40 replaced with D, E, H, K, R, N,

Q, F, W, Y, P, or C; P41 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; W42 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S43 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E44 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C45 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S46 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R47 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C49 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; G50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G52 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y55 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L57 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R58 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R59 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C60 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L61 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S63 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K64 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S65 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C66 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; E67 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G68 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R69 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N70 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I71 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R72 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Y73 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R74 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T75 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C76 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S77 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N78 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V79 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D80 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C81 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or

P;P82 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C;
 P83replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E84
 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A85 replaced
 with D, E,H, K, R, N, Q, F, W, Y, P, or C; G86 replaced with D, E, H, K, R, N, Q, F,
 5 W, Y, P,or C; D87 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or
 C; F88replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R89 replaced
 withD, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A90 replaced with D, E, H,
 K, R,N, Q, F, W, Y, P, or C; Q91 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V,
 F, W,Y, P, or C; Q92 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P,
 10 or C;C93 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P;
 S94replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A95 replaced with D, E, H,
 K, R,N, Q, F, W, Y, P, or C; H96 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F,
 W, Y,P, or C; N97 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or
 C;D98 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
 15 V99replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K100 replaced with D, E, A,
 G, I,L, S, T, M, V, N, Q, F, W, Y, P, or C; H101 replaced with D, E, A, G, I, L, S, T,
 M, V,N, Q, F, W, Y, P, or C; H102 replaced with D, E, A, G, I, L, S, T, M, V, N, Q,
 F, W,Y, P, or C; G103 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q104
 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; F105 replaced
 20 with D, E,H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y106 replaced with D, E, H,
 K, R, N, Q,A, G, I, L, S, T, M, V, P, or C; E107 replaced with H, K, R, A, G, I, L, S,
 T, M, V, N,Q, F, W, Y, P, or C; W108 replaced with D, E, H, K, R, N, Q, A, G, I, L,
 S, T, M, V,P, or C; L109 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P110
 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; V111
 25 replaced with D,E, H, K, R, N, Q, F, W, Y, P, or C; S112 replaced with D, E, H, K, R,
 N, Q, F, W, Y,P, or C; N113 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F,
 W, Y, P, or C;D114 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P,
 or C; P115replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C;
 D116replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N117
 30 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P118 replaced
 with D, E,H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; C119 replaced with D,
 E, H, K,R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S120 replaced with D, E, H, K,

R, N, Q, F, W, Y, P, or C; L121 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K122 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C123 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Q124 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A125 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K126 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G127 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T128 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T129 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L130 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V131 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V132 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E133 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L134 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A135 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P136 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K137 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V138 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L139 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D140 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G141 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T142 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R143 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C144 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Y145 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T146 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E147 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S148 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L149 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D150 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M151 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C152 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; I153 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S154 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G155 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L156 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C157 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Q158 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I159 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V160 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G161 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C162

replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; D163 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H164 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q165 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L166 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G167 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S168 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T169 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V170 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K171 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E172 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D173 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N174 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; C175 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; G176 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V177 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C178 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; N179 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G180 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D181 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G182 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S183 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T184 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C185 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; R186 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L187 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V188 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R189 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G190 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q191 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; Y192 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K193 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S194 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q195 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L196 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S197 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A198 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T199 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K200 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S201 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D202 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F,

W, Y, P, or C; D203 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T204 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V205 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V206 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A207 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I208 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P209 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; Y210 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G211 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S212 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R213 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H214 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I215 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R216 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L217 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V218 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L219 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K220 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G221 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P222 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; D223 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H224 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L225 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y226 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L227 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E228 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T229 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K230 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T231 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L232 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q233 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G234 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T235 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K236 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G237 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E238 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N239 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S240 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L241 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S242 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S243 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T244 replaced with D, E, H, K, R,

N, Q, F, W, Y, P, or C; G245 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
 T246 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F247 replaced with D, E,
 H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L248 replaced with D, E, H, K, R, N, Q,
 F, W, Y, P, or C; V249 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D250
 5 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N251 replaced
 with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S252 replaced with D, E,
 H, K, R, N, Q, F, W, Y, P, or C; S253 replaced with D, E, H, K, R, N, Q, F, W, Y, P,
 or C; V254 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D255 replaced with
 H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; F256 replaced with D, E, H, K,
 10 R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q257 replaced with D, E, H, K, R, A, G, I, L,
 S, T, M, V, F, W, Y, P, or C; K258 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F,
 W, Y, P, or C; F259 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C;
 P260 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C;
 D261 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K262
 15 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E263 replaced with
 H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I264 replaced with D, E, H, K,
 R, N, Q, F, W, Y, P, or C; L265 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
 R266 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M267
 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A268 replaced with D, E, H, K,
 20 R, N, Q, F, W, Y, P, or C; G269 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
 P270 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; L271
 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T272 replaced with D, E, H, K, R,
 N, Q, F, W, Y, P, or C; A273 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
 D274 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; F275
 25 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; I276 replaced with
 D, E, H, K, R, N, Q, F, W, Y, P, or C; V277 replaced with D, E, H, K, R, N, Q, F, W,
 Y, P, or C; K278 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
 I279 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R280 replaced with D, E, A,
 G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N281 replaced with D, E, H, K, R, A, G, I,
 30 L, S, T, M, V, F, W, Y, P, or C; S282 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or
 C; G283 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S284 replaced with D, E,
 H, K, R, N, Q, F, W, Y, P, or C; A285 replaced with D, E, H, K, R, N, Q, F, W, Y, P,

- or C; D286 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
 S287 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T288 replaced with D, E, H,
 K, R, N, Q, F, W, Y, P, or C; V289 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or
 C; Q290 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C;
- 5 F291 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; I292 replaced
 with D, E, H, K, R, N, Q, F, W, Y, P, or C; F293 replaced with D, E, H, K, R, N, Q, A,
 G, I, L, S, T, M, V, P, or C; Y294 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T,
 M, V, P, or C; Q295 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or
 C; P296 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C;
- 10 I297 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I298 replaced with D, E, H,
 K, R, N, Q, F, W, Y, P, or C; H299 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F,
 W, Y, P, or C; R300 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or
 C; W301 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C;
 R302 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E303 replaced
- 15 with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T304 replaced with D, E,
 H, K, R, N, Q, F, W, Y, P, or C; D305 replaced with H, K, R, A, G, I, L, S, T, M, V,
 N, Q, F, W, Y, P, or C; F306 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V,
 P, or C; F307 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C;
 P308 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C;
- 20 C309 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P;
 S310 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A311 replaced with D, E, H,
 K, R, N, Q, F, W, Y, P, or C; T312 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or
 C; C313 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P;
 G314 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G315 replaced with D, E,
- 25 H, K, R, N, Q, F, W, Y, P, or C; G316 replaced with D, E, H, K, R, N, Q, F, W, Y, P,
 or C; Y317 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C;
 Q318 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L319
 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T320 replaced with D, E, H, K,
 R, N, Q, F, W, Y, P, or C; S321 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
- 30 A322 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E323 replaced with H, K,
 R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C324 replaced with D, E, H, K, R, A,
 G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Y325 replaced with D, E, H, K, R, N, Q, A,

G, I, L, S, T, M, V, P, or C; D326 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L327 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R328 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S329 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N330 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R331 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V332 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V333 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A334 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D335 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q336 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; Y337 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; C338 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; H339 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Y340 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y341 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; P342 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E343 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N344 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I345 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K346 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P347 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K348 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P349 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K350 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L351 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q352 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; E353 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C354 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; N355 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L356 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D357 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P358 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; C359 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; P360 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A361 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R362 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W363 replaced with D, E, H, K, R, N, Q, A, G,

I, L, S, T, M, V, P, or C; E364 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A365 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T366 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P367 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; W368 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T369 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A370 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C371 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S372 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S373 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S374 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C375 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; G376 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G377 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G378 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I379 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q380 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S381 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R382 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A383 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V384 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S385 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C386 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; V387 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E388 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E389 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D390 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I391 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q392 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G393 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H394 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V395 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T396 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S397 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V398 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E399 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E400 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W401 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K402 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C403 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; M404 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;

- Y405 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T406 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P407 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K408 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M409 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
- 5 P410 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; I411 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A412 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q413 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P414 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; C415 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P;
- 10 N416 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I417 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F418 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; D419 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C420 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; P421 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K422 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W423 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L424 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A425 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q426 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; E427 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
- 20 C; W428 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S429 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P430 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; C431 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; T432 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V433 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T434 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C435 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; G436 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q437 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G438 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L439 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R440 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Y441 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R442 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V443 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V444 replaced with D, E,

H, K, R, N, Q, F, W, Y, P, or C; L445 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C446 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; I447 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D448 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H449 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R450 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G451 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; M452 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H453 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T454 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G455 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G456 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C457 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S458 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P459 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K460 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T461 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K462 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P463 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; H464 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I465 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K466 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E467 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E468 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C469 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; I470 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V471 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P472 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; T473 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P474 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; C475 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Y476 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K477 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P478 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K479 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E480 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K481 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L482 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P483 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F,

- W,Y, or C; V484 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E485 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A486 replaced with D, E,H, K, R, N, Q, F, W, Y, P, or C; K487 replaced with D, E, A, G, I, L, S, T, M, V, N,Q, F, W, Y, P, or C; L488 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
- 5 P489replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; W490replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F491 replaced withD, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K492 replaced with D, E, A, G, I,L, S, T, M, V, N, Q, F, W, Y, P, or C; Q493 replaced with D, E, H, K, R, A, G, I, L, S,T, M, V, F, W, Y, P, or C; A494 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;Q495 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; E496replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L497 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E498 replaced with H, K, R, A, G, I, L, S,T, M, V, N, Q, F, W, Y, P, or C; E499 replaced with H, K, R, A, G, I, L, S, T, M, V,N, Q, F, W, Y, P, or C; G500 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;A501 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A502 replaced with D, E,H, K, R, N, Q, F, W, Y, P, or C; V503 replaced with D, E, H, K, R, N, Q, F, W, Y, P,or C; S504 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E505 replaced withH, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E506 replaced with H, K, R, A,G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P507 replaced with D, E, H, K, R, A, G, I,L, S, T, M, V, N, Q, F, W, Y, or C; S508 replaced with D, E, H, K, R, N, Q, F, W, Y,P, or C; F509 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; I510replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P511 replaced with D, E, H, K,R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K512 replaced with D, E, A, G, I, L, S,T, M, V, N, Q, F, W, Y, P, or C; A513 replaced with D, E, H, K, R, N, Q, F, W, Y, P,or C; W514 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S515replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A516 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; C517 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N,Q, F, W, Y, or P; T518 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V519replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T520 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; C521 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N,Q, F, W, Y, or P; G522 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V523replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G524 replaced with D, E,

H, K,R, N, Q, F, W, Y, P, or C; T525 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q526 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V527 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R528 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I529 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V530 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R531 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C532 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Q533 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V534 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L535 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;

10 L536 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S537 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F538 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S539 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q540 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S541 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V542 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A543 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D544 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L545 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P546 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; I547 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D548 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;

20 E549 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C550 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; E551 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G552 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P553 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K554 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P555 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A556 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S557 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q558 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R559 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A560 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C561 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Y562 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; A563 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G564 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P565

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replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; C566 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S567 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G568 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E569 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C570 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P571 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E572 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; F573 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; N574 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P575 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; D576 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E577 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T578 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D579 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G580 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L581 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F582 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G583 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G584 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L585 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q586 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; D587 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; F588 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; D589 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E590 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L591 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y592 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; D593 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W594 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E595 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Y596 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E597 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G598 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F599 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T600 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K601 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C602 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S603 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E604 replaced with H,

K,R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S605 replaced with D, E, H, K, R, N,Q, F, W, Y, P, or C; C606 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F,W, Y, or P; G607 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G608 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G609 replaced with D, E, H, K, R, N, Q,F, W, Y, P, or C; V610 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q611 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; E612 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A613 replaced with D, E,H, K, R, N, Q, F, W, Y, P, or C; V614 replaced with D, E, H, K, R, N, Q, F, W, Y, P,or C; V615 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S616 replaced withD, E, H, K, R, N, Q, F, W, Y, P, or C; C617 replaced with D, E, H, K, R, A, G, I, L, S,T, M, V, N, Q, F, W, Y, or P; L618 replaced with D, E, H, K, R, N, Q, F, W, Y, P, orC; N619 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K620replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q621 replaced withD, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; T622 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; R623 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F,W, Y, P, or C; E624 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, orC; P625 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C;A626 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E627 replaced with H, K,R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E628 replaced with H, K, R, A, G, I,L, S, T, M, V, N, Q, F, W, Y, P, or C; N629 replaced with D, E, H, K, R, A, G, I, L, S,T, M, V, F, W, Y, P, or C; L630 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;C631 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; V632replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T633 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; S634 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;R635 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R636replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P637 replaced withD, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; P638 replaced with D, E,H,K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; Q639 replaced with D, E, H, K, R,A, G, I, L, S, T, M, V, F, W, Y, P, or C; L640 replaced with D, E, H, K, R, N, Q, F,W, Y, P, or C; L641 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K642replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S643 replaced withD, E, H, K, R, N, Q, F, W, Y, P, or C; C644 replaced with D, E, H, K, R, A, G, I,

- L, S, T, M, V, N, Q, F, W, Y, or P; N645 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L646 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D647 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P648 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; C649 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; P650 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A651 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R652 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W653 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E654 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
- 10 I655 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G656 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K657 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W658 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S659 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P660 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; C661 replaced with D, E, H, K,
- 15 R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S662 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L663 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T664 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C665 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; G666 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V667 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
- 20 G668 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L669 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q670 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; T671 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R672 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D673 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V674 replaced
- 25 with D, E, H, K, R, N, Q, F, W, Y, P, or C; F675 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; C676 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S677 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H678 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L679 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L680 replaced with D, E, H, K, R, N, Q, F, W,
- 30 Y, P, or C; S681 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R682 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E683 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M684 replaced with D, E, H, K, R, N,

- Q, F, W, Y, P, or C; N685 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; E686 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T687 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V688 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I689 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L690 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A691 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D692 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E693 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L694 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C695 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P;
- 10 R696 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q697 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P698 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; K699 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P700 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S701 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T702 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V703 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q704 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A705 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C706 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; N707 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C;
- 20 R708 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; F709 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; N710 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; C711 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; P712 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; P713 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A714 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; W715 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y716 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; P717 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A718 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q719 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; W720 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q721 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P722 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; C723
- 30

- replaced with D,E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S724 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; R725 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F,W, Y, P, or C; T726 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C727replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P;
- 5 G728replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G729 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; G730 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;V731 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q732 replaced with D, E,H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K733 replaced with D, E, A, G, I, L,S, T, M, V, N, Q, F, W, Y, P, or C; R734 replaced with D, E, A, G, I, L, S, T, M, V, N,Q, F, W, Y, P, or C; E735 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W,Y, P, or C; V736 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L737 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C738 replaced with D, E, H, K, R, A, G, I,L, S, T, M, V, N, Q, F, W, Y, or P; K739 replaced with D, E, A, G, I, L, S, T, M, V, N,Q, F, W, Y, P, or C; Q740 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W,Y, P, or C; R741 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;M742 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A743 replaced with D, E,H, K, R, N, Q, F, W, Y, P, or C; D744 replaced with H, K, R, A, G, I, L, S, T, M, V,N, Q, F, W, Y, P, or C; G745 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;S746 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F747 replaced with D, E,H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L748 replaced with D, E, H, K, R, N, Q,F, W, Y, P, or C; E749 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P,or C; L750 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P751 replaced withD, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E752 replaced with H, K,R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T753 replaced with D, E, H, K, R, N,Q, F, W, Y, P, or C; F754 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P,or C; C755 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P;S756 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A757 replaced with D, E,H, K, R, N, Q, F, W, Y, P, or C; S758 replaced with D, E, H, K, R, N, Q, F, W, Y, P,or C; K759 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
- 25 P760replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A761replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C762 replaced with D, E, H, K,R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Q763 replaced with D, E, H, K,

R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; Q764 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A765 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C766 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; K767 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K768 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D769 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D770 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C771 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; P772 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S773 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E774 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W775 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L776 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L777 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S778 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D779 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W780 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T781 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E782 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C783 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S784 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T785 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S786 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C787 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; G788 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E789 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G790 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T791 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q792 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; T793 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R794 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S795 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A796 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I797 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C798 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; R799 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K800 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M801 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L802 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K803 replaced with D, E, A, G, I,

L, S, T, M, V, N, Q, F, W, Y, P, or C; T804 replaced with D, E, H, K, R, N, Q, F, W,
 Y, P, or C; G805 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L806 replaced
 with D, E, H, K, R, N, Q, F, W, Y, P, or C; S807 replaced with D, E, H, K, R, N, Q, F,
 W, Y, P, or C; T808 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V809
 5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V810 replaced with D, E, H, K,
 R, N, Q, F, W, Y, P, or C; N811 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F,
 W, Y, P, or C; S812 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T813
 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L814 replaced with D, E, H, K, R,
 N, Q, F, W, Y, P, or C; C815 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q,
 10 F, W, Y, or P; P816 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y,
 or C; P817 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C;
 L818 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P819 replaced with D, E, H,
 K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; F820 replaced with D, E, H, K, R,
 N, Q, A, G, I, L, S, T, M, V, P, or C; S821 replaced with D, E, H, K, R, N, Q, F, W, Y,
 15 P, or C; S822 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S823 replaced
 with D, E, H, K, R, N, Q, F, W, Y, P, or C; I824 replaced with D, E, H, K, R, N, Q, F,
 W, Y, P, or C; R825 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or
 C; P826 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C;
 C827 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P;
 20 M828 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L829 replaced with D, E,
 H, K, R, N, Q, F, W, Y, P, or C; A830 replaced with D, E, H, K, R, N, Q, F, W, Y, P,
 or C; T831 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C832 replaced with D,
 E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; A833 replaced with D, E, H,
 K, R, N, Q, F, W, Y, P, or C; R834 replaced with D, E, A, G, I, L, S, T, M, V, N, Q,
 25 F, W, Y, P, or C; P835 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F,
 W, Y, or C; G836 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R837 replaced
 with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P838 replaced with D, E,
 H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S839 replaced with D, E, H, K,
 R, N, Q, F, W, Y, P, or C; T840 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or
 30 C; K841 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
 H842 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S843 replaced
 with D, E, H, K, R, N, Q, F, W, Y, P, or C; P844 replaced with D, E, H, K, R, A, G, I,

L, S, T, M, V, N, Q, F, W, Y, or C; H845 replaced with D, E, A, G, I, L, S, T, M, V,
 N, Q, F, W, Y, P, or C; I846 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
 A847 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A848 replaced with D, E,
 H, K, R, N, Q, F, W, Y, P, or C; A849 replaced with D, E, H, K, R, N, Q, F, W, Y, P,
 5 or C; R850 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
 K851 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V852
 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y853 replaced with D, E, H, K,
 R, N, Q, A, G, I, L, S, T, M, V, P, or C; I854 replaced with D, E, H, K, R, N, Q, F, W,
 Y, P, or C; Q855 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C;
 10 T856 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R857 replaced with D, E, A,
 G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R858 replaced with D, E, A, G, I, L, S, T,
 M, V, N, Q, F, W, Y, P, or C; Q859 replaced with D, E, H, K, R, A, G, I, L, S, T, M,
 V, F, W, Y, P, or C; R860 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P,
 or C; K861 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
 15 L862 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H863 replaced with D, E, A,
 G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; F864 replaced with D, E, H, K, R, N, Q, A,
 G, I, L, S, T, M, V, P, or C; V865 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or
 C; V866 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G867 replaced with D,
 E, H, K, R, N, Q, F, W, Y, P, or C; G868 replaced with D, E, H, K, R, N, Q, F, W, Y,
 20 P, or C; F869 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C;
 A870 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y871 replaced with D, E,
 H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L872 replaced with D, E, H, K, R, N, Q,
 F, W, Y, P, or C; L873 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
 P874 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C;
 25 K875 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T876 replaced
 with D, E, H, K, R, N, Q, F, W, Y, P, or C; A877 replaced with D, E, H, K, R, N, Q, F,
 W, Y, P, or C; V878 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V879
 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L880 replaced with D, E, H, K,
 R, N, Q, F, W, Y, P, or C; R881 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F,
 30 W, Y, P, or C; C882 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W,
 Y, or P; P883 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C;
 A884 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R885 replaced with D, E,

A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R886 replaced with D, E, A, G, I, L, S,
 T, M, V, N, Q, F, W, Y, P, or C; V887 replaced with D, E, H, K, R, N, Q, F, W, Y, P,
 or C; R888 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
 K889 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P890 replaced
 5 with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; L891 replaced with D,
 E, H, K, R, N, Q, F, W, Y, P, or C; I892 replaced with D, E, H, K, R, N, Q, F, W, Y, P,
 or C; T893 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; W894 replaced with
 D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E895 replaced with H, K, R, A, G,
 I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K896 replaced with D, E, A, G, I, L, S, T, M,
 10 V, N, Q, F, W, Y, P, or C; D897 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q,
 F, W, Y, P, or C; G898 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
 Q899 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; H900
 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L901 replaced with
 D, E, H, K, R, N, Q, F, W, Y, P, or C; I902 replaced with D, E, H, K, R, N, Q, F, W,
 15 Y, P, or C; S903 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S904 replaced
 with D, E, H, K, R, N, Q, F, W, Y, P, or C; T905 replaced with D, E, H, K, R, N, Q, F,
 W, Y, P, or C; H906 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or
 C; V907 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T908 replaced with D,
 E, H, K, R, N, Q, F, W, Y, P, or C; V909 replaced with D, E, H, K, R, N, Q, F, W, Y,
 20 P, or C; A910 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P911 replaced
 with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; F912 replaced with D,
 E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G913 replaced with D, E, H, K, R, N,
 Q, F, W, Y, P, or C; Y914 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P,
 or C; L915 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K916 replaced with D,
 25 E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I917 replaced with D, E, H, K, R, N,
 Q, F, W, Y, P, or C; H918 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P,
 or C; R919 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
 L920 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K921 replaced with D, E, A,
 G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P922 replaced with D, E, H, K, R, A, G, I,
 30 L, S, T, M, V, N, Q, F, W, Y, or C; S923 replaced with D, E, H, K, R, N, Q, F, W, Y,
 P, or C; D924 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
 A925 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G926 replaced with D, E,

H, K,R, N, Q, F, W, Y, P, or C; V927 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y928 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T929 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C930 replaced with D, E, H, K,R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S931 replaced with D, E, H, K, R, N, Q,F, W, Y, P, or C; A932 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G933 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P934 replaced with D, E, H, K,R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A935 replaced with D, E, H, K, R, N,Q, F, W, Y, P, or C; R936 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P,or C; E937 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H938 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; F939 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; V940 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I941 replaced with D, E, H, K, R, N, Q, F, W,Y, P, or C; K942 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L943 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I944 replaced with D, E,H, K, R, N, Q, F, W, Y, P, or C; G945 replaced with D, E, H, K, R, N, Q, F, W, Y, P,or C; G946 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N947 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R948 replaced with D, E, A, G,I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K949 replaced with D, E, A, G, I, L, S, T, M,V, N, Q, F, W, Y, P, or C; L950 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V951 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A952 replaced with D, E,H, K, R, N, Q, F, W, Y, P, or C; R953 replaced with D, E, A, G, I, L, S, T, M, V, N,Q, F, W, Y, P, or C; P954 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F,W, Y, or C; L955 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S956 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P957 replaced with D, E, H, K, R, A, G, I,L, S, T, M, V, N, Q, F, W, Y, or C; R958 replaced with D, E, A, G, I, L, S, T, M, V, N,Q, F, W, Y, P, or C; S959 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E960 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E961 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E962 replaced with H, K,R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V963 replaced with D, E, H, K, R, N,Q, F, W, Y, P, or C; L964 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A965 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G966 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; R967 replaced with D, E, A, G, I, L, S, T, M, V,

N, Q, F, W, Y, P, or C; K968 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G969 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G970 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P971 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K972 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E973 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A974 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L975 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q976 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; T977 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H978 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K979 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H980 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q981 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N982 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G983 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I984 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F985 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S986 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N987 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G988 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S989 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K990 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A991 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E992 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K993 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R994 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G995 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L996 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A997 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A998 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N999 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P1000 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G1001 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1002 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1003 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Y1004 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; D1005 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D1006 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1007 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;

V1008 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1009 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1010 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1011 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1012 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1013 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q1014 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G1015 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1016 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; W1017 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; P1018 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; G1019 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1020 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1021 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1022 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1023 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1024 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; W1025 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E1026 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A1027 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1028 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; D1029 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S1030 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1031 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1032 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1033 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N1034 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; T1035 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1036 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1037 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1038 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E1039 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D1040 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1041 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; G1042 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1043 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1044 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q1045 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V1046 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1047 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1048 replaced with D, E,

H, K, R, N, Q, F, W, Y, P, or C; H1049 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1050 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1051 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; F1052 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T1053 replaced with

5 D, E, H, K, R, N, Q, F, W, Y, P, or C; M1054 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1055 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1056 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1057 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q1058 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R1059 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1060 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;

10 L1061 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D1062 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D1063 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I1064 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1065 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1066

15 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N1067 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L1068 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1069 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1070 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; Q1071 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P1072 replaced with D, E,

20 H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E1073 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E1074 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1075 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1076 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D1077 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1078

25 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y1079 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S1080 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K1081 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H1082 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1083 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1084 replaced with D, E, H, K,

30 R, N, Q, F, W, Y, P, or C; A1085 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1086 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L1087 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1088 replaced with D, E, H, K,

R, N, Q, F, W, Y, P, or C; Q1089 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; E1090 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I1091 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F1092 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R1093 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S1094 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H1095 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1096 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1097 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H1098 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q1099 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; D1100 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T1101 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1102 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1103 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K1104 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1105 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S1106 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1107 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1108 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1109 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T1110 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1111 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1112 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; V1113 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1114 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1115 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1116 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1117 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; H1118 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K1119 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H1120 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V1121 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1122 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1123 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F1124 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S1125 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1126 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1127 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1128 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;

R1129 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T1130 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1131 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1132 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1133 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1134 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D1135 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A1136 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1137 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1138 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1139 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1140 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1141 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1142 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1143 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; H1144 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1145 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K1146 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1147 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; T1148 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I1149 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1150 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1151 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K1152 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I1153 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1154 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1155 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1156 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1157 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; Q1158 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L1159 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1160 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1161 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1162 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1163 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V1164 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1165 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1166 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H1167 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1168 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1169 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1170 replaced with D, E, H, K, R, A, G, I, L,

S, T, M, V, F, W, Y, P, or C; T1171 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1172 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1173 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1174 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1175 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1176 replaced
 5 with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1177 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1178 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1179 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1180 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1181 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1182 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1183 replaced with D, E,
 10 H, K, R, N, Q, F, W, Y, P, or C; H1184 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C1185 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; E1186 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A1187 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I1188 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1189 replaced with D, E, H, K, R, N, Q, F, W,
 15 Y, P, or C; H1190 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1191 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R1192 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1193 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; T1194 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I1195 replaced with D, E, H, K,
 20 R, N, Q, F, W, Y, P, or C; S1196 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; W1197 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; A1198 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1199 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N1200 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G1201 replaced with D, E, H, K, R, N, Q, F, W, Y, P,
 25 or C; E1202 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E1203 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V1204 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1205 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; F1206 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S1207 replaced with D, E, H, K, R, N, Q, F, W, Y, P,
 30 or C; D1208 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1209 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I1210 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1211 replaced with D, E, H, K,

R, N, Q, F, W, Y, P, or C; L1212 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1213 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P1214 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; D1215 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D1216 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S1217 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1218 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1219 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I1220 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1221 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1222 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1223 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; V1224 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1225 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A1226 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D1227 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V1228 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1229 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F1230 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y1231 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T1232 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1233 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; N1234 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A1235 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1236 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N1237 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A1238 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1239 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1240 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y1241 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; D1242 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S1243 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1244 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1245 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I1246 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1247 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1248 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1249 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1250 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1251 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1252 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;

K1253 replaced with D,E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1254
 replaced with D, E, H, K, R,A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; L1255
 replaced with D, E, H, K, R, N, Q,F, W, Y, P, or C; V1256 replaced with D, E, H, K,
 R, N, Q, F, W, Y, P, or C; K1257replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F,
 5 W, Y, P, or C; T1258 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1259
 replaced with D, E, H, K, R, N, Q,F, W, Y, P, or C; R1260 replaced with D, E, A, G,
 I, L, S, T, M, V, N, Q, F, W, Y, P,or C; M1261 replaced with D, E, H, K, R, N, Q, F,
 W, Y, P, or C; T1262 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1263
 replaced with D, E, H, K, R, N, Q,F, W, Y, P, or C; I1264 replaced with D, E, H, K,
 10 R, N, Q, F, W, Y, P, or C; N1265replaced with D, E, H, K, R, A, G, I, L, S, T, M, V,
 F, W, Y, P, or C; T1266 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1267
 replaced with H, K, R, A, G, I, L,S, T, M, V, N, Q, F, W, Y, P, or C; K1268 replaced
 with D, E, A, G, I, L, S, T, M, V,N, Q, F, W, Y, P, or C; P1269 replaced with D, E, H,
 K, R, A, G, I, L, S, T, M, V, N,Q, F, W, Y, or C; A1270 replaced with D, E, H, K, R,
 15 N, Q, F, W, Y, P, or C; V1271replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
 T1272 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; V1273 replaced with D, E,
 H, K, R, N, Q, F, W, Y, P, or C;D1274 replaced with H, K, R, A, G, I, L, S, T, M, V,
 N, Q, F, W, Y, P, or C; I1275replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
 G1276 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; S1277 replaced with D, E,
 20 H, K, R, N, Q, F, W, Y, P, or C;T1278 replaced with D, E, H, K, R, N, Q, F, W, Y, P,
 or C; I1279 replaced with D, E,H, K, R, N, Q, F, W, Y, P, or C; K1280 replaced with
 D, E, A, G, I, L, S, T, M, V, N,Q, F, W, Y, P, or C; T1281 replaced with D, E, H, K,
 R, N, Q, F, W, Y, P, or C;V1282 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
 Q1283 replaced with D,E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G1284
 25 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; V1285 replaced with D, E, H, K,
 R, N, Q, F, W, Y, P, or C;N1286 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V,
 F, W, Y, P, or C; V1287replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1288
 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; I1289 replaced with D, E, H, K,
 R, N, Q, F, W, Y, P, or C;N1290 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V,
 30 F, W, Y, P, or C; C1291replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F,
 W, Y, or P; Q1292replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or
 C; V1293 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1294 replaced with

D, E, H, K, R, N, Q, F, W, Y, P, or C; G1295 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1296 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1297 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E1298 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A1299 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1300 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V1301 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1302 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; W1303 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F1304 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R1305 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N1306 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K1307 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S1308 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K1309 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1310 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1311 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1312 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1313 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; H1314 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H1315 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1316 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H1317 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E1318 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G1319 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1320 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1321 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1322 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1323 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1324 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N1325 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V1326 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1327 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1328 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1329 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D1330 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q1331 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G1332 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1333 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y1334 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S1335

replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1336 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; R1337 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A1338 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1339 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N1340 replaced with

5 D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L1341 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H1342 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G1343 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1344 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1345 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1346 replaced with D, E, H, K,

10 R, N, Q, F, W, Y, P, or C; E1347 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S1348 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1349 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1350 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L1351 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1352 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I1353

15 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1354 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D1355 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1356 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; P1357 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; Q1358 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C;

20 V1359 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1360 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; T1361 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1362 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L1363 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1364 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D1365

25 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I1366 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1367 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A1368 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1369 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1370 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1371 replaced with D, E, H, K, R, N, Q, F, W,

30 Y, P, or C; A1372 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1373 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1374 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1375 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q,

F, W, Y, or C; N1376 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L1377 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1378 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S1379 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1380 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1381 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1382 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1383 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1384 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; L1385 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1386 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1387 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1388 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L1389 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1390 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1391 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D1392 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1393 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; G1394 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N1395 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S1396 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1397 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1398 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1399 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1400 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1401 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; P1402 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; I1403 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K1404 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G1405 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H1406 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1407 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; V1408 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1409 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; N1410 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I1411 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1412 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; W1413 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F1414 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; H1415 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;

- G1416 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1417 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1418 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P1419 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; I1420 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
- 5 V1421 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1422 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1423 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1424 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1425 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1426 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1427 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H1428 replaced
- 10 with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H1429 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I1430 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1431 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1432 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1433 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1434 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1435 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I1436 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1437 replaced
- 15 with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1438 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V1439 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1440 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N1441 replaced
- 20 with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L1442 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1443 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1444 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1445 replaced
- with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1446 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1447 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G1448 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1449 replaced
- 25 with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; F1450 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S1451 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1452 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L1453 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
- 30 A1454 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1455 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N1456 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; E1457 replaced with H, K, R, A, G, I, L, S, T,

M, V, N, Q, F, W, Y, P, or C; A1458 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1459 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1460 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1461 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; M1462 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1463
5 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K1464 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A1465 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1466 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1467 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1468 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I1469 replaced with D, E, H, K, R, N, Q, F, W,
10 Y, P, or C; Q1470 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; D1471 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Y1472 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; W1473 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; W1474 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S1475 replaced with D, E, H,
15 K, R, N, Q, F, W, Y, P, or C; V1476 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D1477 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1478 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1479 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1480 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1481 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
20 C1482 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S1483 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1484 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1485 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1486 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; G1487 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N1488 replaced with
25 D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R1489 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G1490 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1491 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1492 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; Q1493 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P1494 replaced
30 with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R1495 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1496 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1497 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F,

- W, Y, P, or C; C1498 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L1499 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1500 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N1501 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S1502 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1503 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1504 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V1505 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N1506 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P1507 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A1508 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
- 10 H1509 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C1510 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; A1511 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1512 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K1513 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V1514 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1515
- 15 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1516 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A1517 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1518 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1519 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P1520 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C;
- 20 I1521 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1522 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1523 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; N1524 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R1525 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1526 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;
- 25 D1527 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C1528 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; P1529 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S1530 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1531 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W1532 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; M1533 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1534 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1535 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1536 replaced with D, E, H, K, R, N, Q, F, W,
- 30

Y, P, or C; W1537 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S1538 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1539 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1540 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; T1541 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;

5 R1542 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S1543 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1544 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; G1545 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1546 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1547 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1548 replaced with D, E,

10 H, K, R, N, Q, F, W, Y, P, or C; Q1549 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; T1550 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1551 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1552 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V1553 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1554 replaced with D, E, H, K, R, N, Q,

15 F, W, Y, P, or C; C1555 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Q1556 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K1557 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1558 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K1559 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A1560 replaced with D, E, H, K, R, N, Q, F,

20 W, Y, P, or C; S1561 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1562 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I1563 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1564 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1565 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1566 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; V1567 replaced with D, E, H, K,

25 R, N, Q, F, W, Y, P, or C; S1568 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N1569 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; D1570 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M1571 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1572 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; T1573 replaced with D, E, H, K, R, N,

30 Q, F, W, Y, P, or C; Q1574 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V1575 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1576 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K1577 replaced with D, E, A, G,

I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1578 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1579 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; V1580 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D1581 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T1582 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1583 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A1584 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1585 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; N1586 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; Q1587 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; Q1588 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L1589 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1590 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; V1591 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1592 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W1593 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; A1594 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F1595 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S1596 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1597 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; W1598 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G1599 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1600 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; C1601 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; N1602 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G1603 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1604 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; C1605 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; I1606 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G1607 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1608 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; H1609 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1610 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1611 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1612 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1613 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; H1614 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1615 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;

- Q1616 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V1617 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F1618 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; C1619 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Q1620 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; T1621 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1622 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D1623 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G1624 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I1625 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1626 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1627 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1628 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S1629 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1630 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q1631 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; C1632 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S1633 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A1634 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1635 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1636 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R1637 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1638 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; V1639 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1640 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1641 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1642 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N1643 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; C1644 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; W1645 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S1646 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1647 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A1648 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1649 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S1650 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1651 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H1652 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W1653 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R1654 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;

V1655replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1656 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; L1657 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;W1658 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T1659replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L1660 replaced with D, E, H, K,R, N, Q, F, W, Y, P, or C; C1661 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V,N, Q, F, W, Y, or P; T1662 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;A1663 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1664 replaced with D,E, H, K, R, N, Q, F, W, Y, P, or C; C1665 replaced with D, E, H, K, R, A, G, I, L, S,T, M, V, N, Q, F, W, Y, or P; G1666 replaced with D, E, H, K, R, N, Q, F, W, Y, P,or C; N1667 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C;Y1668 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G1669replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F1670 replaced with D, E, H, K,R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q1671 replaced with D, E, H, K, R, A, G, I, L,S, T, M, V, F, W, Y, P, or C; S1672 replaced with D, E, H, K, R, N, Q, F, W, Y, P, orC; R1673 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R1674replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V1675 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1676 replaced with H, K, R, A, G, I, L,S, T, M, V, N, Q, F, W, Y, P, or C; C1677 replaced with D, E, H, K, R, A, G, I, L, S,T, M, V, N, Q, F, W, Y, or P; V1678 replaced with D, E, H, K, R, N, Q, F, W, Y, P, orC; H1679 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A1680replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1681 replaced with D, E, A, G,I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T1682 replaced with D, E, H, K, R, N, Q, F,W, Y, P, or C; N1683 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P,or C; K1684 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C;A1685 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V1686 replaced with D,E, H, K, R, N, Q, F, W, Y, P, or C; P1687 replaced with D, E, H, K, R, A, G, I, L, S,T, M, V, N, Q, F, W, Y, or C; E1688 replaced with H, K, R, A, G, I, L, S, T, M, V, N,Q, F, W, Y, P, or C; H1689 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y,P, or C; L1690 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1691 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; S1692 replaced withD, E, H, K, R, N, Q, F, W, Y, P, or C; W1693 replaced with D, E, H, K, R, N, Q, A,G, I, L, S, T, M, V, P, or C; G1694 replaced with D, E, H, K, R, N, Q, F, W, Y, P, orC;

P1695 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R1696 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P1697 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; A1698 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N1699 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; W1700 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q1701 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R1702 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C1703 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; N1704 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I1705 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1706 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P1707 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; C1708 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; E1709 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N1710 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; M1711 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E1712 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C1713 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; R1714 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D1715 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T1716 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1717 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1718 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Y1719 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; C1720 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; E1721 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K1722 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V1723 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K1724 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q1725 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L1726 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K1727 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L1728 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1729 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; Q1730 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L1731 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S1732 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q1733

replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; F1734 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K1735 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S1736 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R1737 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C1738 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; C1739 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; G1740 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T1741 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C1742 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; G1743 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K1744 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; or A1745 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The resulting constructs can be routinely screened for activities or functions described throughout the specification and known in the art. Preferably, the resulting constructs have an decreased THRAP activity or function, while the remaining THRAP activities or functions are maintained. More preferably, the resulting constructs have more than one decreased THRAP activity or function, while the remaining THRAP activities or functions are maintained.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to: prostate cancer, cancer of the gastrointestinal tract, disorders of the uterus, neurological disorders, synovial sarcoma, immune disorders, tumor growth, and/or cancer, in general. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above

tissues or cells, particularly of the immune, neural, gastrointestinal, bone, skeletal, connective, and/or reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neural, gastrointestinal, bone, skeletal, connective, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, semen, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more of the immunogenic epitopes shown in SEQ ID NO: 89 as residues: Cys-3 to Pro-9, Arg-24 to Leu-35, Pro-41 to Gly-50, Lys-64 to Ser-77, Cys-93 to His-102, Ser-112 to Cys-119, Thr-142 to Ser-148, Val-170 to Gly-176, Arg-189 to Gln-195, Thr-235 to Leu-241, Arg-300 to Asp-305, Tyr-325 to Asn-330, Pro-342 to Asn-355, His-449 to Cys-457, Pro-459 to Lys-466, Pro-474 to Leu-482, Lys-492 to Leu-497, Glu-549 to Ser-557, Phe-573 to Gly-580, Tyr-596 to Cys-606, Asn-619 to Glu-627, Ser-634 to Leu-640, Trp-653 to Trp-658, Cys-695 to Ser-701, Pro-722 to Cys-727, Ala-765 to Ser-773, Thr-781 to Arg-794, Pro-835 to Pro-844, Thr-856 to Lys-861, Pro-883 to Arg-888, Leu-955 to Glu-960, Arg-967 to Ile-984, Asn-987 to Gly-995, Pro-1000 to Leu-1007, Gln-1028 to Gly-1042, Thr-1056 to Asp-1062, Leu-1068 to Tyr-1079, Pro-1105 to Ser-1111, Leu-1128 to Thr-1148, Arg-1305 to Gly-1311, Ser-1327 to Gly-1332, Cys-1486 to Arg-1495, Cys-1523 to Ser-1530, Gly-1666 to Arg-1674, Arg-1681 to Val-1686, Pro-1695 to Asn-1704, Pro-1707 to Arg-1718, Gln-1733 to Cys-1738. Polynucleotides encoding these polypeptides are also encompassed by the invention. Antibodies that bind one or more of these epitopes, domains described herein, or other polypeptides of the invention are specifically, but nonexclusively preferred.

The ubiquitous tissue distribution, the homology to thrombospondin-related protein, and the presence of multiple TSP-1-like domains indicates that the THRAP polypeptide and/or fragments of the present invention possess anti-angiogenic activity and, therefore, can be used in the treatment, diagnosis, and/or prevention of solid tumors of many tissues including, but not limited to the prostate, lung, breast, ovarian,

stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer. Additionally, the THRAP polypeptide and/or fragments of the present invention can be used in the treatment, diagnosis, and/or prevention of primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias.

Additionally, the THRAP polypeptide and/or fragments of the present invention possess anti-angiogenic activity and, therefore, can be used in the treatment, diagnosis, and/or prevention of other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, restenosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and/or atherosclerosis.

Moreover, the ubiquitous tissue distribution and the presence of proteinase inhibitor-like domains indicates that the THRAP polypeptide and/or fragments of the present invention are useful as a proteinase inhibitor.

The tissue distribution in brain and homology to thrombospondin-related protein indicates that the THRAP polypeptide and/or fragments of the present invention are useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of

Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive
5 compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it may play a role in normal neural function. Potentially, THRAP polypeptide and/or fragments of the present invention may be involved in synapse
10 formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival.

The tissue distribution in immune cells and tissues (e.g., macrophage, and lymph node) and homology to thrombospondin-related protein indicates that the THRAP polypeptide and/or fragments of the present invention are useful for the
15 detection, treatment, and/or prevention of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this THRAP polypeptide and/or fragments of the present invention indicates a role in regulating the proliferation; survival; differentiation;
20 and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an
25 agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host
30 diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may

represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The expression within fetal tissue and other cellular sources marked by proliferating cells and homology to thrombospondin-related proteins indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus the THRAP polypeptide and/or fragments of the present invention may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The THRAP polypeptide and/or fragments of the present invention are useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The THRAP polypeptide and/or fragments of the present invention can also be used to gain new insight into the regulation of cellular growth and proliferation.

Additionally, the secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, and as nutritional supplements. It

may also have a very wide range of biological activities. Representative uses are described in the "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the THRAP polypeptide and/or fragments of the present invention may possess the following activities: cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines; immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Polynucleotides of the invention may also be employed in gene therapy. Representative uses of gene therapy are described in the section "Gene Therapy" below and elsewhere herein.

Additionally, the expression of this gene product in synovium and homology to thrombospondin-related protein would suggest a role in the detection and treatment of disorders and conditions afflicting the skeletal system, in particular osteoporosis, bone cancer, connective tissue disorders (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation). The THRAP polypeptide and/or fragments of the present invention are also useful in the diagnosis or treatment of various autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, and dermatomyositis), dwarfism, spinal deformation, joint abnormalities, and chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid, etc.). Furthermore, the THRAP polypeptide and/or fragments of the present invention may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein

may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. However, preferably excluded from the present invention includes Genseq accession numbers Y35899, X97684, and X97583 (WO/9931236), which are hereby incorporated by reference in its entirety. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 5706 of SEQ ID NO:18, b is an integer of 15 to 5720, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 9

The translation product of this gene shares sequence homology with the mouse uterine-specific proline-rich acidic protein which may play an important role in pregnancy. Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with proline-rich acidic proteins. Such activities are known in the art, some of which are described elsewhere herein.

This gene is expressed primarily in colon cancer and to a lesser extent in fetal liver and spleen.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to: colon cancer; digestive disorders; hematopoietic disorders; immune system dysfunction; inflammation; inflammatory bowel disease. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological

probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the colon and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes shown in SEQ ID NO: 90 as residues: Trp-35 to Trp-45, Pro-52 to Asp-57, Thr-73 to Thr-80, Pro-96 to Leu-103, Pro-106 to Arg-118, Pro-131 to Gln-142. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution in colon cancer cells and tissues, combined with the homology to the mouse proline-rich acidic protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and/or treatment of disorders of the colon, including colon cancer. Elevated levels of this transcript in various colon tumors suggests that it may represent an important diagnostic or causative agent in the development or progression of colon cancer. Alternately, expression in the colon may be indicative of roles in normal colon or digestive function. Similarly, expression of this transcript in hematopoietic cells and tissues, such as fetal liver suggests that it may play a role in the proliferation, differentiation, survival, or activation of a variety of blood cell lineages. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 691 of SEQ ID NO:19, b
5 is an integer of 15 to 705, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 10

The translation product of this gene shares sequence homology with bovine
10 vacuolar ATP synthase membrane sector associated protein (see, e.g., Genbank Accession No. sp|P81134|VATN_BOVIN; all references available through this accession are hereby incorporated by reference in their entirety herein). Vacuolar ATPase is composed of at least 10 subunits and is believed to be responsible for acidifying a variety of intracellular compartments in eukaryotic cells.

15 The polypeptide encoded by this gene has been determined to have a transmembrane domain at about amino acid position 307 to about 323 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing about amino acids 324 to about 350 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of
20 this gene shares structural features to type Ia membrane proteins.

It has been discovered that this gene is expressed primarily in dendritic cells, human osteoclastoma, placenta, fetal liver spleen, infant brain, colon tumor, pancreatic tumor, and ovarian tumor.

Therefore, nucleic acids of the invention are useful as reagents for differential
25 identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: immune, skeletal, developmental, reproductive, and/or neural diseases or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders
30 of the above tissues or cells, particularly of the immune, hematopoietic, and/or integumentary system(s), expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., immune, skeletal,

developmental, reproductive, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

5 Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 91 as residues: Gln-153 to Ser-163, Ser-172 to Glu-178, Ala-204 to Asp-210, Ile-222 to Ala-236, Lys-284 to Ser-291, Met-342 to Arg-348. Polynucleotides encoding said polypeptides are also encompassed by the invention.

10 The tissue distribution in immune cells and tissues indicates that polynucleotides and/or polypeptides corresponding to this gene would be useful for the treatment, prevention, detection and/or diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages.

15 Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. Polynucleotides and/or polypeptides of the invention may also be involved

20 in lymphopoiesis, and therefore, would be useful in treating, preventing, detecting and/or diagnosing immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

25 Alternatively, polynucleotides and/or polypeptides corresponding to this gene would be useful in detecting, diagnosing, treating, and/or preventing congenital disorders (i.e., nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e., keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis

30 fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e., wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e., lupus erythematosus, vitiligo,

dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e., cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Moreover, the protein product of this clone may also be useful for the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma, tendonitis, chondromalacia and inflammation, etc.), autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, and chondrodysplasias (i.e., spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). The predicted membrane localization indicates that polynucleotides and/or polypeptides corresponding to this gene would be a good target for antagonists, particularly small molecules or antibodies, which block functional activity (such as, for example, transport function; complex formation; binding of the receptor by its cognate ligand(s); signalling function). Accordingly, preferred are antibodies and or small molecules which specifically bind an extracellular portion of the translation product of this gene. The extracellular regions can be ascertained from the information regarding the transmembrane domains as set out above. Also provided is a kit for detecting tumors in which expression of this protein occurs (such as, for example, ovarian cancer). Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional

supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
 5 related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the
 10 general formula of a-b, where a is any integer between 1 to 2094 of SEQ ID NO:20, b is an integer of 15 to 2108, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 11**

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group consisting of: MKPATASALLLLLGLAWTQGSHGWGADASSLQKRAGRADQPGAGWQEVA (SEQ ID NO: 176), MKPATASALLLLLGLAWTQGSHGWGADASSLQKRA
 20 GRADQPGAGWQEVA AVTSKNYNYNQHAYPTA (SEQ ID NO: 177), MKPATASALLLLLGLAWTQGSHGWGADASSLQKRAGRADQPGAGWQEVA AVTSKNYNYNQHAYPTAYGGKYSVKTPAKGGVS (SEQ ID NO: 178), and MAGGGSCNFQELQLQPACVSHCLWWEVLSQDPCKGGSLTFFLGFPGATWPAAVGÈVL VGNFLQPPPRPRKALVVRELLPLAPSLCQPWPGCHTSVS (SEQ ID NO: 179).

25 Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide
 30 encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by

the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in fetal heart, healing wounds, and keratinocytes.

5 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to: developmental, cardiovascular, and integumentary diseases and/or disorders, particularly vascular disorders and impaired wound healing. Similarly, polypeptides
10 and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the integumentary and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developmental, cardiovascular,
15 integumentary, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 92 as residues: Ser-31 to Gly-45, Ser-54 to Gln-61, Ala-67 to Val-74. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution in fetal heart indicates that polynucleotides and
25 polypeptides corresponding to this gene are useful for the detection and/or treatment of vascular disorders including heart disease, myocardial infarction, ischemia, stroke, tumorogenesis, wound healing, ulcerative colitis, and skin disorders including psoriasis.

The tissue distribution in keratinocytes and healing wounds indicates that the
30 protein product of this clone is useful for the treatment, diagnosis, and/or prevention of various skin disorders. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", "Infectious Disease", and "Regeneration"

sections below, in Example 11, 19, and 20, and elsewhere herein. Briefly, the protein is useful in detecting, treating, and/or preventing congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e. wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm).

Moreover, the protein product of this clone may also be useful for the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma, tendonitis, chondromalacia and inflammation, etc.), autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, and chondrodysplasias (i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 661 of SEQ ID NO:21, b is an integer of 15 to 675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 12

Translation products corresponding to this gene share sequence homology with sodium hydrogen exchanger proteins(See, e.g., Genbank Accession AAC39643), which are thought to be involved in the electroneutral exchange of protons for Na⁺ and K⁺ across the mitochondrial inner membrane contributing to organellar volume and Ca²⁺ homeostasis Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with sodium hydrogen exchanger proteins. Such activities are known in the art, some of which are described elsewhere herein.

The polypeptide of this gene has been determined to have potential transmembrane domains at about amino acid position 19-35, 50-66, 158-174, 201-217, 235-251, 271-285, 320-336, 387-403, 430-446, and 456-472 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIb membrane proteins.

In a specific embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise, or alternatively consist of the following amino acid sequence:

RPRLGSSSGAAAEDSSAMEELATEKEAEESHQRQDSVXLLTFILLTLTILTIWLF
 25 KHRRVRFLHETGLAMIYGLIVGVILRYGTPATSGRDKSLCTQEDRAFSTLLV
 NVSGKFFEYTLKGEISPGKINSVEQNMLRKVTFDPEVFFNILLPPIIFHAGYSL
 KKRHFFRNLSILAYAF LGTAXSCFIIGNLMYGVVKLMKIMGQLSDKFYTYX
 XLFFGAIISATDPVTVLAIFNELHADVDLYALLFGESVLNDAVAIXLXSSIVAY
 QPAGLNTHAFDAAFFKSVGIFLGIFSGSFTMGAVTGVTAXVTKFTKXHXFP
 30 LLETALFFLMSWSTFLLAEACGFTGVVAVLFCGITQAHYTYNNLSVESRSRTK
 QLFEVLHFLAENFIFS YMGLALFTFQKHVFSPIFIIGAFVAIFLGRAAHYPLSFF
 LNLGRRHKIGWNFQHMMMFSGLRGAMAFALAIRDTASYARQMMFTTTLLIV

FFTVWIIG GGTTPMLSWLNIRVGVDPDXXDPPXXDSFAFXTETA (SEQ ID NO: 180). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in germinal center B cell, and other cells of the immune system (e.g., thymus stromal cells, bone marrow stromal cells, dendritic cells and T cells) and to a lesser extent in stromal cells and brain.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: including arthritis, asthma, immunodeficiency diseases and leukemia. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 93 as residues: Leu-4 to Ser-18. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The homology of this gene to a sodium/hydrogen exchanger protein suggests that this gene is involved in cellular metabolism and maintaining Calcium

homeostasis. The balance of calcium in the cell is extremely important with regards to signal transduction. Thus, expression of this gene in cells of the immune and nervous systems indicates that this gene may have a role in helping cells respond to extracellular signals to proliferate, differentiate, migrate, survive or die. Accordingly, the polynucleotides and/or polypeptides corresponding to this gene (and/or antibodies raised against those polypeptides) would be useful for treatment/detection of immune disorders such as arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia, allergy, graft rejection, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other autoimmune conditions, infections, chronic variable immune deficiency (CVID) and other immune deficiency syndromes, respiratory distress syndrome and inflammation, neoplasms of the immune/hematopoietic system including leukemias, lymphomas and other proliferative disorders such as multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma, and myelodysplastic syndromes.

Further, the expression of this gene in the nervous system of the human indicates that the polynucleotides and/or polypeptides corresponding to this gene, (and/or antibodies raised against those polypeptides) are useful in the detection, diagnosis and treatment of neurological conditions such as manic depression, Alzheimer's, Huntington's, and Parkinson's disease, Tourettes's syndrome and other neurodegenerative diseases including but not limited to, demyelinating diseases, epilepsy, headache, migraine, CNS infections, neurological trauma and neural regrowth following trauma, CNS neoplasms, stroke and reperfusion injury following stroke. It may also be useful for the treatment and diagnosis of learning and cognitive diseases, depression, dementia, psychosis, mania, bipolar syndromes, schizophrenia and other psychiatric conditions. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival.

The polynucleotides and/or polypeptides corresponding to this gene (and/or antibodies raised against those polypeptides) would be useful for in the treatment/detection of thymus disorders such as Graves Disease, thyroiditis, hyperthyroidism and hypothyroidism; and in the treatment

pineal gland disorders such as the circadian rhythm disturbances associated with shift work, jet lag, blindness, insomnia and old age.

Based upon the tissue distribution of this protein, antagonists directed against this protein may be useful in blocking the activity of this protein. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene. Also provided is a kit for detecting tumors in which expression of this protein occurs. Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1567 of SEQ ID NO:22, b is an integer of 15 to 1581, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 13

The translation product of this gene shares sequence homology with a novel protein with a calcium binding motif (See, e.g., Genbank Accession number J30027) which may be important in calcium mediated signaling events. Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with calcium binding proteins. Such activities are known in the art, some of which are described elsewhere herein.

In a specific embodiment, polypeptides comprising the amino acid sequence of the open reading frame upstream of the predicted signal peptide are contemplated by the present invention. Specifically, polypeptides of the invention comprise, or alternatively consist of the following amino acid sequence:

NGKISPYWWEQKLELHRGGGRSRTSGSPGLQEFGTSRGRAFWGRGLVRLTLE
GFASASETVRILMTMRSLLRTPFLCGLLWAFCAPGARAEPAASFQPGSMGL
DKNTVHDQEHIMEHLEGVINKPEAEMSPQELQLHYFKMHDYDGNLLDGLE
LSTAITHVHKEEGSEQAPLMSEDELINIIDGVLRDDDKNNDGYIDYAEFAKSL
Q (SEQ ID NO: 181). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group consisting of: MLHDMLLVVHCVLIQAHAAAGLGEAGCRLLSPGAWGTKGPEQATQEGGSEQ GSHGHQYPYGLRSRREALQREPHQPPSPKRSSSARAEFLQPGGSTSSRAAATA VELQLLFPIVRGDFXV (SEQ ID NO: 182) and MTPSRCSMICSWSCFVFLSRPMLPGWE KLAAGSSALAPGAQKAQSRPHRKGVLRSRDLMVINILTVSEADAKPSNVSLTSP RPQNALPRLVPNSCSPG DPLVLERPPPRWSSSFCSQ (SEQ ID NO: 183). Polynucleotides encoding these polypeptides are also encompassed by the invention.

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

It has been discovered that this gene is expressed primarily in bone marrow stroma and arthritic bone and to a lesser extent in pregnant uterus, retina, brain, dendritic cells and several other tissues and cell lines.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: osteoporosis, osteoarthritis or other bone related diseases. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system and blood forming tissues, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 94 as residues: Ala-24 to Pro-29, Asp-42 to Glu-50, Asp-81 to Asn-86, Lys-102 to Gln-108, Arg-126 to Tyr-135. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution and homology to calcium binding proteins suggests that the protein product of this clone would be useful for diagnosis, treatment and monitoring of diseases of the bone and joints including osteoporosis, osteoarthritis, bone cancers, and diseases of the bone marrow leading to alterations in the cells of the

circulatory system. Based upon the tissue distribution of this protein, antagonists directed against this protein may be useful in blocking the activity of this protein. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene. Also provided is a kit for detecting tumors in which expression of this protein occurs. Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 908 of SEQ ID NO:23, b is an integer of 15 to 922, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 14

The translation product of this gene appears to be the human homolog of a mouse interferon-gamma (IFN-g)-induced protein expressed in peritoneal macrophages (see GenBank accession AAA66219, and Lafuse et al. (J. Leukocyte

Biol. 57(3):477-83). When tested against T-cells, polypeptides of the present invention stimulated IL-5 release.

It has been discovered that this gene is expressed in bone marrow, activated T-cells and monocytes, as well as in fetal tissues, placenta, infant brain, corneal stromal cells, and a number of cancerous tissues (including ovary and colon cancers, and T-cell lymphoma).

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: neurological, immune and hematopoietic disorders as well as developmental and proliferative disorders, including cancer. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, haemopoietic and central nervous system, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., bone marrow, neural, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 95 as residues: Met-1 to Ala-28, Pro-40 to Glu-48, Ile-68 to Ile-73, Gly-183 to Glu-188, Pro-286 to Ser-295, Val-301 to Gly-307, Asp-311 to His-321.

Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution and homology to a mouse interferon-induced gene suggests that the protein product of this clone would be useful for treatment and diagnosis of disorders of the immune and hematopoietic systems, as well as neurological disorders, including epilepsy, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder,

learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Based upon the tissue distribution of this protein, antagonists directed against this protein may be useful in blocking the activity of this protein. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene. Also provided is a kit for detecting tumors in which expression of this protein occurs. Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a

solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. The expression of this gene in highly proliferative tissues (e.g. fetus, placental, infant brain, cancers) suggests that translation products of this gene may be involved in cell differentiation and/or proliferation. Therefore, protein, as well as antibodies directed against the protein, may show utility as tumor markers and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2274 of SEQ ID NO:24, b is an integer of 15 to 2288, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 15

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 3-19 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 20-81 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
SGXPGSTHASAHASQLPSQDVKICLLTMRLLVLSLLCILLLCFSIFSTEGKRR

PAKAWSGRRLRLCCHRVSPNSTNLKGHHVRLCKPCKLEPEPRLWVVPGLPQV (SEQ ID NO: 184). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

10 This gene is expressed primarily in colon and to a lesser extent in prostate, dendritic cells, healing groin wound, keratinocytes, and ovary.

 Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to:

15 gastrointestinal system, colorectal cancer, reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal system, reproductive and immune system expression of this gene at significantly

20 higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the

25 disorder.

 Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 96 as residues: Thr-22 to Cys-40, Val-44 to His-56. Polynucleotides encoding said polypeptides are also encompassed by the invention.

30 The tissue distribution in colon, colon cancer and ovary tumor indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis, treatment and/or detection of tumors, especially of the intestine, such as, carcinoid

tumors, lymphomas, cancer of the colon and cancer of the rectum, as well as cancers of the ovary and other tissues where the expression has been indicated. The expression in the colon and ovary tissues, and immune cells may indicate the gene or its products can be used to treat and/or diagnose other disorders of the gastrointestinal,

5 reproductive, and immune including inflammatory disorders such as, diverticular colon disease (DCD), inflammatory colonic disease, Crohn's disease (CD), non-inflammatory bowel disease (non-IBD) colonic inflammation; ulcerative disorders such as, ulcerative colitis (UC), amebic colitis, eosinophilic colitis; noncancerous tumors, such as, polyps in the colon, adenomas, leiomyomas, lipomas, and angiomas.
10 Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence
20 would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 894 of SEQ ID NO:25, b is an integer of 15 to 908, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

25

FEATURES OF PROTEIN ENCODED BY GENE NO: 16

This gene is expressed primarily in developing lung, hemangiopericytoma and merkel cells.

Polynucleotides and polypeptides of the invention are useful as reagents for
30 differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to: disorders of the skin, peripheral neuropathy, diseases of the lung, and cancers,

particularly of the connective tissues (for example, involving pericytes) and soft tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skin, pulmonary, and peripheral nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pulmonary, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 97 as residues: Ala-55 to Ser-60. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution in Merkel cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment of disorders involving sensory innervation such as peripheral neuropathy and sensory loss associated with leprosy. Moreover, the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse

formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival.

Alternatively, the protein is useful for the treatment of disorders involving loss of lung function such as emphysema, ARDS, and cystic fibrosis. The protein is also useful for the treatment, detection, and/or prevention of pain disorders. The tissue distribution in Merkel cells also indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment of disorders involving: the skin (particularly, but not limited to, skin cancer); the lungs (for example lung cancer); and pericytes (particularly, but not limited to, hemangiopericytoma). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2076 of SEQ ID NO:26, b is an integer of 15 to 2090, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 17

A supernatant from a transfection of this gene has been shown to induce transcription in Jurkat T-cells by the SEAP assay. Specifically, when tested against Jurkat T-cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activating sequence) promoter element. Thus, it is likely that this gene activates T-cells, and to a lesser extent, in immune and hematopoietic cells and tissue

cell types, through the Jak-Stat signal transduction pathway. GAS is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

MWGWGSLVSARGGWGVFIYLYMGLYIVLWGMGEPAGGENPPLSPHPPGRA

10 NVKLLIFVLYIFYINISIFFLQNQFINGRGVWGGHMELPLWGGPLHYPTYRPF

HPPPHSPPPGDCCKMGV (SEQ ID NO: 185). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein,

polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to

these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in neurological tissue (including cerebellum, adult brain, epileptic frontal cortex, corpus colosum, and fetal brain) and to a lesser extent in T-cells and other immunological tissues, as well as a variety of tumors and other normal adult and fetal tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to: neural diseases and/or disorders, particularly cancer and other proliferative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g.,

lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

5 Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 98 as residues: Thr-52 to Phe-62, Pro-130 to Arg-135, Pro-160 to Arg-173, Thr-190 to His-195, Gly-246 to Arg-252, Arg-397 to Thr-403, Gly-414 to Arg-420, Arg-483 to Glu-488. Polynucleotides encoding said polypeptides are also
10 encompassed by the invention.

The tissue distribution in neurological tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of cancer and other proliferative disorders, particularly of neural and immune tissues. Representative uses are described in the "Regeneration" and "Hyperproliferative
15 Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction,
20 aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product
25 is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the
30 protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2341 of SEQ ID NO:27, b is an integer of 15 to 2355, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 18

Supernatants from cells expressing this gene stimulate T cells and or NK cells to secrete interferon-gamma. Interferon gamma is an immunomodulatory cytokine that, for example, regulates inflammation and inhibits Th2 immune responses.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group consisting of: GTRYAAASPAWAAAQQRSH PAMSPGTPGPTMGRSQGSPMDPMVMKRPQLY GMGSNPHSQPQQSSPYPGGSYGPPGPQRYPIGIQGRTPGAMAGMQYPQQQMP PQYGQQGVSGYCQQGQQPYYSQQPQPPHLPQAQYLPSQSQQRYQPQQVST VHCPAGPVFSTKADPALNHLPVLY (SEQ ID NO: 186), PSFSASAEQSVPRRFLWPSRPTAVSNWHPGSDSRGHGRNAVPSAADATSVWT ARCEWLLPAGPTAILQPAAAAPAPPTPGAVSAVPVPAEVPAAAGEHSALPRRP CFLHQGRPGSESSSCPLLKIMFWWKKN (SEQ ID NO: 187), and/or MIQSRVCLGGENRACGAVHCAHLLRLVPLLGLGRQILRLGWEVRGLRLLAVI WLLALLAVTTHLLSILRWHLRLVHSGHGPSPTLDANWIPLWAWRAIGT SWVRTALLRLRMRVTAHAIQRLSLHHHWIHWAAALGSAHGRSGGAGAHRRV TPLLGRPGRAGSGVPRA (SEQ ID NO: 188). Polynucleotides encoding these polypeptides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to

these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in glioblastoma and fetal tissues (including fetal heart, fetal lung and fetal liver/spleen) and to a lesser extent in retina, germinal center B cells (from chronic lymphocytic leukemia and germinal center), and apoptotic T-cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to: neural, developmental, and immune diseases and/or disorders, particularly cancer and other proliferative disorders, including glioblastoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and fetal tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developmental, immune, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in neural tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of cancer and other proliferative disorders, particularly of the brain and fetal tissue. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia,

trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Alternatively, the expression within developmental tissues indicates that the protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions.

Additionally, the homology of the ability of this gene to stimulate the secretion of interferon-gamma indicates that the polynucleotides and/or polypeptides corresponding to this gene (and/or antibodies raised against those polypeptides) are useful for the diagnosis and treatment of diseases and disorders associated with the immune system, including, but not limited to, allergy, asthma, graft rejection, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other autoimmune conditions, infections, AIDS, chronic variable immune deficiency (CVID) and other immune deficiency syndromes, respiratory distress syndrome and inflammation, neoplasms of the immune/hematopoietic system including leukemias, lymphomas and other proliferative disorders such as multiple myeloma, Hodgkin's and non-Hodgkin's lymphoma, and myelodysplastic syndromes. The polynucleotides and/or polypeptides corresponding to this gene (and/or antibodies raised against those polypeptides) may also be useful for stimulating the immune response to bolster the immune response to diseases such as cancer or infection.

Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1666 of SEQ ID NO:28, b is an integer of 15 to 1680, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 19

Contact of MVEC cells with supernatant expressing the product of this gene was shown to increase the expression of a soluble adhesion molecule, specifically, ICAM-1. Thus it is likely that the product of this gene is involved in the activation of MVEC, in addition to other endothelial cell-lines or tissue cell types. Thus, polynucleotides and polypeptides related to this gene have uses which include, but are not limited to, activating vascular endothelial cells, such as during an inflammatory response.

The polypeptide encoded by this gene has been determined to have a transmembrane domain at about amino acid position 61 to about 77 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing about amino acids 1 to about 60 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type II membrane proteins.

It has been discovered that this gene is expressed primarily in Soares infant brain 1NIB and to a lesser extent in normalized infant brain cDNA.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: neurodevelopmental and/or neurodegenerative diseases or disorders. Similarly, polypeptides and antibodies

directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g.,
5 nervous, neural, neuronal, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, lymph, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively
10 consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 100 as residues: Leu-27 to Glu-32. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution in fetal brain indicates that polynucleotides and/or polypeptides corresponding to this gene would be useful for the detection, diagnosis,
15 treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, diagnosis, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease,
20 Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including
25 disorders in feeding, sleep patterns, balance, and perception.

In addition, elevated expression of polynucleotides and/or polypeptides corresponding to this gene in regions of the brain indicates that polynucleotides and/or polypeptides of the invention may play a role in normal neural function. Potentially, polynucleotides and/or polypeptides of the invention are involved in synapse
30 formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival.

The predicted membrane localization indicates that polynucleotides and/or polypeptides corresponding to this gene would be a good target for antagonists, particularly small molecules or antibodies, which block functional activity (such as, for example, binding of the receptor by its cognate ligand(s); transport function; signalling function). Accordingly, preferred are antibodies and or small molecules which specifically bind an extracellular portion of the translation product of this gene. The extracellular regions can be ascertained from the information regarding the transmembrane domains as set out above. Also provided is a kit for detecting tumors in which expression of polynucleotides and/or polypeptides corresponding to this gene occurs. Such a kit comprises in one embodiment an antibody specific for polynucleotides and/or polypeptides corresponding to this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1604 of SEQ ID NO:29, b is an integer of 15 to 1618, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 20

The translation product of this gene shares sequence homology with, and is believed to be a novel homolog of, GDNF. GDNF, neurturin (see, e.g., Genbank Accession No. gb|AAC50898.1|; all references available through this accession are hereby incorporated in their entirety by reference herein), persephin (see, e.g.,
10 Genbank Accession No. gb|AAC39640.1| (AF040962); all references available through this accession are hereby incorporated in their entirety by reference herein) and related family members serve useful roles as survival factors for neurons, particularly dopaminergic neurons. They can also have neurotrophic effects on neurons. GDNF and Neurturin (NTN) can each activate the MAP kinase signalling
15 pathway in cultured sympathetic neurons and support the survival of sympathetic neurons, as well as of sensory neurons of the nodose and dorsal root ganglia. Persephin, like GDNF and NTN, promotes the survival of ventral midbrain dopaminergic neurons in culture and prevents their degeneration after 6-hydroxydopamine treatment in vivo. Persephin also supports the survival of motor
20 neurons in culture and in vivo after sciatic nerve axotomy and, like GDNF, promotes ureteric bud branching. However, in contrast to GDNF and NTN, persephin does not support peripheral neurons. Fibroblasts transfected with Ret and one of the coreceptors GFRalpha-1 or GFRalpha-2 do not respond to persephin, suggesting that persephin utilizes additional, or different, receptor components than GDNF and NTN.
25 For these reasons, they may play key roles in mediating outcome of neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS) and Parkinson's disease. Potentially, it may turn out that GDNF-like molecules (i.e., novel family members) will exert survival, proliferation, or trophic effects on other cell types besides neurons. Thus, based on the sequence similarity, the translation product
30 of this clone is expected to share at least some biological activities with GDNF family member proteins. Such activities are known in the art, some of which are described elsewhere herein.

It has been discovered that this gene is expressed primarily in smooth muscle.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: neural and vascular diseases
5 and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, PNS, and vascular systems, expression of this gene at significantly higher or lower levels may be detected in certain tissues (e.g., vascular,
10 neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively
15 consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 101 as residues: Pro-75 to Cys-84. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The homology to GDNF indicates that polynucleotides and/or polypeptides corresponding to this gene would be useful for the detection, diagnosis, treatment,
20 and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, diagnosis, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease,
25 Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including
30 disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse

formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 959 of SEQ ID NO:30, b is an integer of 15 to 973, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 21

The translation product of this clone shares sequence homology to the NADH oxidoreductase complex I subunit of *Caenorhabditis elegans* (See Genbank Accession No. gi|5019819|gb|AAD37863.1|AF143152_1 and Nucleic Acids Res. 27 (17), 3424-3432 (1999); all information contained within this accession and publication is hereby incorporated herein by reference). Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with NADH oxidoreductase proteins. Such activities are known in the art, some of which are described elsewhere herein.

The polypeptide of this gene has been determined to have five transmembrane domains at about amino acid position 62 - 78, 95 - 111, 113 - 129, 149 - 165, and 169

- 185 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane proteins.

5 A preferred polypeptide fragment of the invention comprises the following amino acid sequence:
MTLFGLFVSLVFLGQAFTIMLVYVWSRRNPYVRMNFGLLNFAQPFLPWVL
MGFSLLLGNSIIVDLLGIAVGHIYFFLEDVFPNQPGGIRILKTPSILKAIFDTPDE
DPNYNPLPEERP GGFAWGEGQRLGG (SEQ ID NO: 189). Polynucleotides
encoding these polypeptides are also provided.

10 This gene is expressed primarily in fetal liver spleen and to a lesser extent in most tissues and/or cell types examined.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to:
15 hematopoietic and immune diseases and/or disorders, particularly multiple myeloma, leukemia, and hemophilia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic systems, expression of
20 this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic, immune, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the
25 expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes shown in SEQ ID NO: 102 as residues: Gly-88 to Arg-93, Ser-133 to Tyr-138, Phe-189 to Gly-195,
30 Thr-211 to Gly-227. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution enrichment in fetal liver spleen indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or detection of immune and/or hematopoietic disorders including arthritis, asthma, immunodeficiency diseases, leukemia, transplant rejection, and microbial infections. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Additionally this gene's homology to the NADH oxidoreductase complex I subunit protein indicates that this gene may play a role in cellular metabolism. Thus, the polynucleotides and/or polypeptides corresponding to this gene (and/or antibodies raised against those polypeptides) may be useful in detecting, diagnosing, and or treating complex I deficiencies. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional

supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
 5 related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the
 10 general formula of a-b, where a is any integer between 1 to 1175 of SEQ ID NO:31, b is an integer of 15 to 1189, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 22**

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

HASALALGPPGAAAPWPRPGCSSASAPPTPASAPWPASPSSSSGRWSTDSRGP
 RLMGGLAGVLALWVLVTHVMYMQDYWRTWLKGLRGFFFVGVLFSAVSIAA
 20 FCTFLVLAITRHQSLTDPTSYYLSSVWSFISFKWAFL
 LSLYAHRYRADFADISILSDF (SEQ ID NO: 192) and
 CTCKIIGGPGSRGCAASSSWASSSRPSPSLPSAPSSCWPSPGIRASQTPPATTPA
 SGASFPSSGPPSCSASMPTATGLTLLTSASSAISDPGGEVSAPWGGLRTWTQPLR
 CWERLLPPPGDPRTVAENTQQDECGLPGSCPARPLSRKPECGREGLPCCSSA
 25 WPEGSFRPFQMNLFSLFSLFFFLFFFLRWSLTLSPRLECSSAISAHCNLRLPGSS
 NSPALASQVAGITGICHARQIFVFLVETGFCHVGQAGLELLISGDSPASAFQS
 AGIIGVSHRARP GSVFLARSEESLYLRPGQQSQEVKV (SEQ ID NO: 190),
 MRPGPMLQARVSIPAALGTLFPRPGWAPGEVSSEISSRDLLNPHPSTPSCCSQS
 WSPMSVLEPDSRGPPPISLTHGTGHTPQKTSQMRPDSGSRGMCFCPCCKGFGE
 30 GNIVEAGKSPQTCAHAPPALRFHSAFSEGPCCTQTTGQERPCLPLQPLSLPFN
 (SEQ ID NO: 191),
 MPTATGLTLLTSASSAISDPGGEVSAPWGGLRTWTQPLRCWERLLPPPGDPRT

VAENTQQDECGLPGSCPARPLSRKPECGREGILPCCSSSAWPEGSFRPFQMNL
FSFLSFFFLFFFFLWSLTLSPRLECSSAISAHCNLRLLPGSSNSPALASQVAGITG
ICHHARQIFVFLVETGFCHVGQAGLELLISGDSPASAFQSAGIIGVSHRARPGS
VFLARSEESLYLRPGQQSQEVKV (SEQ ID NO: 193), and

5 MAPSRLQLGLRAAYSGISSVAGFSIFLVWTVVYRQPGTAAHGRARRGAGTVG
PGDARNVHARLLEDLAQGAARLLLGRPLLRLLHRLHLLPRAGHHPASEPH
RPHQLLPLQRLELHFLQVGLPAQPLCPPLPG (SEQ ID NO: 194). Moreover,
fragments and variants of these polypeptides (such as, for example, fragments as
described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or
10 99% identical to these polypeptides and polypeptides encoded by the polynucleotide
which hybridizes, under stringent conditions, to the polynucleotide encoding these
polypeptides, or the complement thereof are encompassed by the invention.
Antibodies that bind polypeptides of the invention are also encompassed by the
invention. Polynucleotides encoding these polypeptides are also encompassed by the
15 invention.

This gene is expressed primarily in Soares adult brain N2b4HB55Y and to a
lesser extent in epididymus, soares testis NHT, macrophage, and dendritic cells,
placenta, tonsils, helper T-cells, embryo, and amniotic cells.

Polynucleotides and polypeptides of the invention are useful as reagents for
20 differential identification of the tissue(s) or cell type(s) present in a biological sample
and for diagnosis of diseases and conditions which include but are not limited to:
neurodegenerative and immune disorders. Similarly, polypeptides and antibodies
directed to these polypeptides are useful in providing immunological probes for
differential identification of the tissue(s) or cell type(s). For a number of disorders of
25 the above tissues or cells, particularly of the central nervous system and immune
system, expression of this gene at significantly higher or lower levels may be
routinely detected in certain tissues or cell types (e.g., neural, immune, cancerous and
wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal
fluid) or another tissue or sample taken from an individual having such a disorder,
30 relative to the standard gene expression level, i.e., the expression level in healthy
tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 103 as residues: Tyr-2 to Trp-7, Arg-42 to Thr-50. Polynucleotides encoding said polypeptides are also encompassed by the invention.

5 The tissue distribution in brain indicates the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not
10 limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive
15 disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis,
20 or neuronal differentiation or survival.

 The tissue distribution in immune cells (e.g., T-cells and macrophage) indicates the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14,
25 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting
30 immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency

diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1898 of SEQ ID NO:32, b is an integer of 15 to 1912, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 23

The translation product of this gene shares sequence homology with zinc finger proteins (see, e.g., Genbank Accession numbers CAA17278.1 and AAC51180; all references available through this accession are hereby incorporated by reference

herein.). Additionally, the translation product of this gene shares sequence homology with OTIC 18 brain-specific nucleosome assembly protein and BRCA1-associated protein (see, e.g., Genseq accession numbers W37504 and W52187, respectively) which are important for diagnosis or therapy of hereditary disease and cancers, particularly of the brain, ovaries, and breast.

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, an amino acid sequence selected from the group:

PRVRGKGKKIFIHMHEIIQIDGHIYQCLECKQNFCEALALIMCQRTHTGEKPYK
CDMCEKTFVQSSDLTSHQRIHNYEKPYKCSKCEKSFWHHLALSQHQRTHAG
KKFYTCDICGKNFGQSSDLLVHQRSHTGEKPYLCSECDKCFSRSTNLIRHRRRT
HTGEKPFKCLDVKKLLVGNQILLATRELTGKGPTNVISVRKVTDTVQPSLYI
KEFILGRSPISVEPVKNALARNQTLVHQRVHTGEKPYKCLECMRSFTRSANLI
RHQATHHTFKCLEYEKSFNCSSRSNCTSVEFTWKRTPTSVVWRLESGFLLRN
GLCCPTRK (SEQ ID NO: 195) and

MHEIIQIDGHIYQCLECKQNFCEALALIMCQRTHTGEKPYKCDMCEKTFVQSS
DLTSHQRIHNYEKPYKCSKCEKSFWHHLALSQHQRTHAGKKFYTCDICGKNF
GQSSDLLVHQRSHTGEKPYLCSECDKCFSRSTNLIRHRRRTHTGEKPFKCLECE
KAFSGKSDLISHQRTHTGERPYKCNKCEKSYRHRSAFIVHKRVHTGEKPYKC
GACEKCFGQKSDLIVHQRVHTGEKPYKCLECMRSFTRSANLIRHQATHHTF
KCLEYEKSFNCSRSNCTSVEFTWKKTPTSVVWRLESGFLLRNLCCPTRK

(SEQ ID NO: 196). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in brain frontal cortex, ovary, skin, dendritic cells, skin, bone marrow and to a lesser extent in colon.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include but are not limited to: ovarian cancer, brain cancer, neurodegenerative and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For
5 a number of disorders of the above tissues or cells, particularly of the central nervous system, ovaries, colon, and immune cells, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, ovarian, neural, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken
10 from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain and homology to OTIC 18 indicates the protein product of this clone is useful for the detection, treatment, and/or prevention of
15 neurodegenerative disease states, behavioral disorders, inflammatory conditions, or brain cancer. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease,
20 Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including
25 disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The tissue distribution in ovaries and homology to
30 BRCA1-associated protein indicates that polynucleotides and polypeptides corresponding to this gene are useful for detection, treatment, and/or prevention of ovarian and/or breast cancer.

The tissue distribution in bone marrow and dendritic cells indicates the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2380 of SEQ ID NO:33, b
 5 is an integer of 15 to 2394, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 24

10 The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 2-18 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 19-49 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib
 15 membrane proteins.

Preferred polypeptides comprise the following amino acid sequence:

GTRERGLRTPQMVLVFAYLCVLLIVCWVTSKLSLALKYTVYKNFKRLIWNKS
 ILIITLTP (SEQ ID NO: 197). Also preferred are the polynucleotides encoding these polypeptides.

20 This gene is expressed primarily in brain frontal cortex

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to: neurological conditions. Similarly, polypeptides and antibodies directed to these
 25 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, cancerous and wounded tissues) or bodily fluids (e.g., serum,
 30 plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level,

i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in brain indicates the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2104 of SEQ ID NO:34, b is an integer of 15 to 2118, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 25

The translation product of this gene shares sequence homology with Alix from *Mus musculus*, which is thought to be important in activation of apoptosis. According to Vito, et. al, *J.Biol Chem* (1999) Mouse ALIX (or AIP1 according to the authors' nomenclature) interacts with ALG-2 and is required for the calcium dependent step of

10 apoptosis.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of the following amino acid sequence selected from the group consisting of:

VGAPGKLDPERRRSASLSASQSASPPAQYLSLLGPRKLSAVCLARTAAEALI
 15 MATFISVQLKKTSEVDLAKPLVKFIQQTYPSSGGEEQAQYCRAAEELSKLRRAA
 VGRPLDKHEGALETLLRYYDQICSIEPKFPFSENQICLTFTWKDAFDKGSFLGG
 SVKLALASLGYEKSCVLFNCAALASQIAAEQNLDNDEGLKIAAKHYQFASGA
 FLHIKETVLSALSREPTVDISPDTVGTLSLIMLAXAQEVFFLKATRDKMKDAIL
 AKLANQAADYFGDAFKQCQYKDTLPKEVFPVLAAKHCIMQANAEYHQSI
 20 KQKKKFGEIARLQHAAELIKTVASRYDEYVNVKDFSDKINRALXAAKKDND
 FIYHDRVDPDLKDLDPGKATLVKSTPVNVPISQKFTDLFEKMVPVSVQQSLAA
 YNQRKADLVNRSIAQMREATTLANGVLASNLPAAIEDVSGDTPVQSILTKSR
 SVIEQGGIQTVDQLIKELPELLQRNREILDESLRLLDEEEATDNDLRAKFKERW
 QRTPSNELYKPLRAEGTNFRTVLDKAVQADGQVKECYQSHRDTIVLLCKPEP
 25 ELNAAIPSANPAKTMQGSEVVXVLKSLLSNLDEVKKEREGLNDLKSVMFDM
 TSKFLTALAQDGVINEEALSVTELDRVYGGLTTKVQESLKKQEGLLKNIQVSH
 QEFKMKQSNNEANLREEVLKLNLATAYDNFVELVANLKEGTFKYNELTEILV
 RFQNKCSDIVFARKTERDELLKDLQQSIAREPSAPSIPTPAYQSLPAGGHAPTPP
 TPAPRTMPPTKPQPPARPPPPVLPANRAPSATAPSPVGAGTAAPAPSQTPGSAP
 30 PPQAQGPPYPTYPGYPGYCQMPMPMGYNPYAYGQYNMPYPPVYHQSPGQAP
 YPGPQQPSYFPF QPPQQSYYPQQ (SEQ ID NO: 199). Polynucleotides encoding
 these polypeptides are also encompassed by the invention. Moreover, fragments and

variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In specific embodiments, polypeptides of the invention comprise, or alternatively consist of the following amino acid sequence:

MHQLQLQRQEPCRLSPSPQPLHHLCFQOI
ELLLLLLHLQWGLGLLRQLHHKRLAQLLHRRRDHPIPIQDILGIAKCPCPW
AILMRMASIICHIIHC
ITRVLDRLRTRDPSSLHTPSLSPHSSLTIHSSNMSAQQLS (SEQ ID NO: 198).

Polynucleotides encoding these polypeptides are also encompassed by the invention.

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in prostate cancer, osteoblasts, microvascular endothelial cells, umbilical vein, breast, fetal cochlea, pancreas tumor, fetal heart, testes, 8 week whole embryo, fetal liver spleen, and primary dendritic cells and to a lesser extent in a variety of normal and transformed adult and fetal tissues and cell lines.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample

and for diagnosis of diseases and conditions which include but are not limited to: vascular, hematopoietic, reproductive, and developmental diseases and/or disorders, particularly cancer and other proliferative disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the prostate skeletal system, breast, pancreas, testes, and the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., vascular, hematopoietic, and developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, amniotic fluid, seminal fluid, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 106 as residues: Thr-28 to Gln-36, Gln-138 to Gly-145. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution in microvascular endothelial cells and umbilical vein, combined with the homology to the Alix protein, a factor which is required for apoptosis, indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment and diagnosis of cancer and other proliferative disorders, especially prostate cancer, since such a protein product could potentially be used to induce programmed cell death in tumors. Moreover, this protein may represent a protein which is constitutively down regulated in proliferative cells and tissues, and primarily in vascular tissues. Thus, agonizes of this protein may inhibit vascularization in tumors by returning the cellular control of this protein to basal, non-transformed levels. Moreover, the protein is useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological

activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence
10 would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 6051 of SEQ ID NO:35, b is an integer of 15 to 6065, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a
15 + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 26

In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:

20 VAVSNNSQAQVTWNLGAALCSGSQWLPERASAKCEMRGHITLLTTSFLVFG
LHIIF LNI SCFNFRVFILFETRPEDSRLYRERPVLPRY (SEQ ID NO: 200).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the
25 polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

30 The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 13-29 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 30-56

of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

This gene is expressed primarily in fetal tissue (e.g., liver, spleen), prostate,
5 brain, colon, bone marrow and T-cells.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to: developmental, immune, and neurodegenerative disorders. Similarly, polypeptides
10 and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, immune, cancerous and
15 wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively
20 consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 107 as residues: Thr-39 to Leu-53. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution in brain indicates the protein product of this clone is useful for the detection, treatment, and/or prevention of neurodegenerative disease
25 states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis,
30 encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive

disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival.

The tissue distribution in immune cells (e.g., T-cells) and bone marrow indicates the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Moreover, the expression within fetal tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular

division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental
5 tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of
10 potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types
15 of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new
20 insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or
25 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
30 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 1351 of SEQ ID NO:36, b is an integer of 15 to 1365, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 27

This invention relates to newly identified Lipocolon polynucleotides, polypeptides encoded by such polynucleotides, the use of such polynucleotides and polypeptides, as well as the production of such polynucleotides and polypeptides. The polypeptide of the present invention has been putatively identified as a human lipocalin homolog derived from colon carcinoma cDNA library. More particularly, the polypeptide of the present invention has been putatively identified as a human lipocalin colon carcinoma-derived protein, sometimes hereafter referred to as "Lipocolon" and/or "LPC". The invention also relates to inhibiting the action of such polypeptides.

The lipocalin protein family is a large group of small extracellular proteins. The family demonstrates great diversity at the sequence level, though most lipocalins share three characteristic conserved sequence motifs. The kernel lipocalins represent a more divergent family member as they share only a single conserved sequence motif. Belying this sequence dissimilarity, lipocalin crystal structures are highly conserved and comprise a single eight-stranded continuously hydrogen-bonded antiparallel beta-barrel, which encloses an internal ligand-binding site. Together with two other families of ligand-binding proteins, the fatty-acid-binding proteins (FABPs) and the avidins, the lipocalins form part of an overall structural superfamily: the calycins.

Members of the lipocalin family are characterized by several common molecular-recognition properties: the ability to bind a range of small hydrophobic molecules, binding to specific cell-surface receptors and the formation of complexes with soluble macromolecules. The varied biological functions of the lipocalins are mediated by one or more of these properties. In the past, the lipocalins have been classified as transport proteins; however, it is now clear that the lipocalins exhibit great functional diversity, with roles in retinol transport, invertebrate cryptic coloration, olfaction and pheromone transport, and prostaglandin synthesis. These

general properties suggest such proteins as appropriate transporters transferring biologically hazardous molecules in a safe and controlled manner between cells. Moreover, many lipocalins have been implicated in the regulation of cell homeostasis: apolipoprotein D, quiescence specific protein, purpurin, alpha-1-microglobulin, and
5 NGAL. This combination of direct and indirect evidence indicates that the lipocalin protein family is involved, in a quite general way, in the mediation of cell regulation and that many presently functionless family members might act in this way.

The lipocalins have also been implicated in the regulation of cell homeostasis and the modulation of the immune response, and, as carrier proteins, to act in the
10 general clearance of endogenous and exogenous compounds. Roles for lipocalins in cell regulation have been proposed. Recently, NGAL (Neutrophil gelatinase-associated lipocalin) has been attributed to the pathogenesis of certain pathologic conditions in the colonic mucosa (See Nielsen BS, et al., Gut Mar;38(3):414-20; which is hereby incorporated herein). Interestingly, NGAL was found in a variety of
15 normal and pathological human tissues. Neoplastic human tissues showed a very heterogeneous expression of NGAL protein. High NGAL levels were found in adenocarcinomas of lung, colon and pancreas. In contrast, renal cell carcinomas of various subtypes and prostate cancers contained low NGAL levels. Lymphomas and thymic tumours were negative for NGAL immuno-labeling.

20 Certain lipocalins are able to induce strong allergic responses. The molecular mimicry between lipocalin allergens and endogenous lipocalins at the T-cell level may explain why the immune response against lipocalins is Th2-dominated and results in allergy. This view is supported by recent studies of autoimmune and parasitic diseases and peptide analogues. The literature has intriguing references to
25 members of the lipocalin family. For example, experiments have shown that the serum measurement of a protein from the neutrophil, human neutrophil lipocalin (HNL), is a superior means to distinguish acute bacterial and viral infections. Prostaglandin (PG) D2 is recognized as the most potent endogenous sleep-promoting substance whose action mechanism is the best characterized among the various sleep-substances thus
30 far reported. Lipocalin-type PGD synthase is dominantly produced in the arachnoid membrane and choroid plexus of the brain, and is secreted into the CSF to become beta-trace, a major protein component of the CSF. The PGD synthase as well as the

PGD2 thus produced circulates in the ventricular system, subarachnoidal space, and extracellular space in the brain system. PGD2 then interacts with DP receptors in the chemosensory region of the ventro-medial surface of the rostral basal forebrain to initiate the signal to promote sleep probably via the activation of adenosine A2A receptive neurons.

The polypeptide of the present invention has been putatively identified as a member of the lipocalin family and has been termed Lipocolon ("LPC"). This identification has been made as a result of amino acid sequence homology to lipocalin of *Bufo marinus*, prostaglandin D synthase, and cpl-1 proteins of *Xenopus laevis*, in combination with its isolation from a human colon carcinoma cDNA library.

Figure 1 shows the nucleotide (SEQ ID NO:37) and deduced amino acid sequence (SEQ ID NO:201) of LPC. Predicted amino acids from about 48 to about 62 constitute the predicted lipocalin motif II (amino acid residues from about 48 to about 62 in SEQ ID NO:201) and are represented by the underlined amino acid regions; amino acids from about 77 to about 92 constitute the lipocalin motif III (amino acid residues from about 77 to about 92 in SEQ ID NO:201) and are represented by the double underlined amino acids.

Figure 2 shows the regions of similarity between the amino acid sequences of the Lipocolon (LPC) protein (SEQ ID NO:201), the lipocalin of *Bufo marinus*, emb|CAA48138.1 (SEQ ID NO: 202); the *Xenopus* prostaglandin D synthase, dbj|BAA12075.1 (SEQ ID NO: 203); and the *Xenopus* cpl-1 proteins, emb|CAA59132.1 (SEQ ID NO: 204).

Figure 3 shows an analysis of the Lipocolon (LPC) amino acid sequence. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown.

A polynucleotide encoding a polypeptide of the present invention is obtained from human colon adenocarcinoma, colon carcinoma, and cervical adenocarcinoma tissues, in addition to HeLa S3 cell line cells. The polynucleotide of this invention was discovered in a human colon carcinoma cDNA library. Its translation product has homology to the characteristic lipocalin domains. As shown in Figure 1 and Figure 2, LCP has two lipocalin domains (the lipocalin domains comprise amino acids 48 - 62 and/or 77 - 92 of SEQ ID NO:201; which correspond to amino acids 48 ñ 62 and/or

77 - 92 of Figure 1) with strong conservation between other members of the lipocalin family. The polynucleotide contains an open reading frame encoding a portion of the LPC polypeptide of 123 amino acids. LCP exhibits a high degree of homology at the amino acid level to the lipocalin of *Bufo marinus*, prostaglandin D synthase and cpl-1 proteins of *Xenopus laevis* (as shown in Figure 2).

The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding the LCP polypeptide having the amino acid sequence shown in Figure 1 (SEQ ID NO:201), which was determined by sequencing a cloned cDNA, gene HWNFG66. The nucleotide sequence shown in Figure 1 (SEQ ID NO:37) was obtained by sequencing a cDNA gene (HWNFG66), which was deposited on September 27, 1999 at the American Type Culture Collection, and given Accession Number PTA-797. The deposited gene (HWNFG66) is inserted in the pSport plasmid (Life Technologies, Rockville, MD) using the *SalI*/*NotI* restriction endonuclease cleavage sites.

The present invention is further directed to fragments of the isolated nucleic acid molecules described herein. By a fragment of an isolated DNA molecule having the nucleotide sequence of the deposited cDNA or the nucleotide sequence shown in SEQ ID NO:37 is intended DNA fragments at least about 15nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 50-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of the deposited cDNA or as shown in SEQ ID NO:37. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of the deposited cDNA or the nucleotide sequence as shown in SEQ ID NO:37 (Figure 1). In this context "about" includes the particularly recited size, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Representative examples of LCP polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251

to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, from about 501 to about 550, from about 551 to about 570, from about 1 to about 236, from about 144 to about 188, from about 231 to about 276 of SEQ ID NO:37 (Figure 1), or the complementary strand thereto, or the cDNA contained in the deposited gene. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Preferred nucleic acid fragments of the present invention include nucleic acid molecules encoding a member selected from the group: a polypeptide comprising or alternatively, consisting of, any one of the lipocalcin domains (amino acid residues from about 48 to about 62 and/or 77 to about 92 in Figure 1 (amino acids from about 48 to about 62 and/or 77 to about 92 in SEQ ID NO:201). Since the location of these domains have been predicted by computer analysis, one of ordinary skill would appreciate that the amino acid residues constituting these domains may vary slightly (e.g., by about 1 to 15 amino acid residues) depending on the criteria used to define each domain.

In additional embodiments, the polynucleotides of the invention encode functional attributes of LCP. Preferred embodiments of the invention in this regard include fragments that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions of LCP.

The data representing the structural or functional attributes of LCP set forth in Figure 3 and/or Table 8, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 8 can be used to determine regions of LCP which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an

environment in which antigen recognition may occur in the process of initiation of an immune response.

Certain preferred regions in these regards are set out in Figure 3, but may, as shown in Table 8, be represented or identified by using tabular representations of the data presented in Figure 3. The DNA*STAR computer algorithm used to generate Figure 3 (set on the original default parameters) was used to present the data in Figure 3 in a tabular format (See Table 8). The tabular format of the data in Figure 3 is used to easily determine specific boundaries of a preferred region.

The above-mentioned preferred regions set out in Figure 3 and in Table 8 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in Figure 1. As set out in Figure 3 and in Table 8, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and Hopp-Woods hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions.

Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, etc.) may still be retained. For example, the ability of shortened LCP muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that an LCP mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six LCP amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues deleted from the amino terminus of the LCP amino acid sequence shown in Figure 1, up to the proline residue at position number 117 and

polynucleotides encoding such polypeptides. In particular, the present invention provides polypeptides comprising the amino acid sequence of residues n1-123 of Figure 1, where n1 is an integer from 2 to 117 corresponding to the position of the amino acid residue in Figure 1 (which is identical to the sequence shown as SEQ ID NO:201).

In another embodiment, N-terminal deletions of the LCP polypeptide can be described by the general formula n2-123, where n2 is a number from 2 to 117, corresponding to the position of amino acid identified in Figure 1. N-terminal deletions of the LCP polypeptide of the invention shown as SEQ ID NO:201 (Figure 1) include polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues: I-2 to P-117; R-3 to P-117; P-4 to P-117; T-5 to P-117; E-6 to P-117; E-7 to P-117; G-8 to P-117; G-9 to P-117; L-10 to P-117; H-11 to P-117; V-12 to P-117; H-13 to P-117; M-14 to P-117; E-15 to P-117; F-16 to P-117; P-17 to P-117; G-18 to P-117; A-19 to P-117; D-20 to P-117; G-21 to P-117; C-22 to P-117; N-23 to P-117; Q-24 to P-117; V-25 to P-117; D-26 to P-117; A-27 to P-117; E-28 to P-117; Y-29 to P-117; L-30 to P-117; K-31 to P-117; V-32 to P-117; G-33 to P-117; S-34 to P-117; E-35 to P-117; G-36 to P-117; H-37 to P-117; F-38 to P-117; R-39 to P-117; V-40 to P-117; P-41 to P-117; A-42 to P-117; L-43 to P-117; G-44 to P-117; Y-45 to P-117; L-46 to P-117; D-47 to P-117; V-48 to P-117; R-49 to P-117; I-50 to P-117; V-51 to P-117; D-52 to P-117; T-53 to P-117; D-54 to P-117; Y-55 to P-117; S-56 to P-117; S-57 to P-117; F-58 to P-117; A-59 to P-117; V-60 to P-117; L-61 to P-117; Y-62 to P-117; I-63 to P-117; Y-64 to P-117; K-65 to P-117; E-66 to P-117; L-67 to P-117; E-68 to P-117; G-69 to P-117; A-70 to P-117; L-71 to P-117; S-72 to P-117; T-73 to P-117; M-74 to P-117; V-75 to P-117; Q-76 to P-117; L-77 to P-117; Y-78 to P-117; S-79 to P-117; R-80 to P-117; T-81 to P-117; Q-82 to P-117; D-83 to P-117; V-84 to P-117; S-85 to P-117; P-86 to P-117; Q-87 to P-117; A-88 to P-117; L-89 to P-117; K-90 to P-117; A-91 to P-117; F-92 to P-117; Q-93 to P-117; D-94 to P-117; F-95 to P-117; Y-96 to P-117; P-97 to P-117; T-98 to P-117; L-99 to P-117; G-100 to P-117; L-101 to P-117; P-102 to P-117; E-103 to P-117; D-104 to P-117; M-105 to P-117; M-106 to P-117; V-107 to P-117; M-108 to P-117; L-109 to P-117; P-110 to P-117; Q-111 to P-117; or S-112 to P-117; of SEQ ID NO:201 (Figure 1). Polypeptides encoded by these polynucleotides are also encompassed by the invention. Moreover,

fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention.

Antibodies that these bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities (e.g., ability to illicit mitogenic activity, induce differentiation of normal or malignant cells, bind to retinal, bind to retinoic acid, ability to bind small lipophilic molecules, etc.), ability to multimerize, ability to bind small lipophilic molecules receptors may still be retained. For example the ability of the shortened LCP mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that an LCP mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six LCP amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the LCP polypeptide shown in Figure 1, up to the glutamine residue at position number 7, and polynucleotides encoding such polypeptides. In particular, the present invention provides polypeptides comprising the amino acid sequence of residues 1-m1 of Figure 1, where m1 is an integer from 7 to 117 corresponding to the position of the amino acid residue in Figure 1.

Moreover, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, the amino acid sequence of C-terminal deletions of the LCP polypeptide of the invention shown as SEQ ID NO:201 (Figure 1) include polypeptides comprising the amino acid sequence of residues: A-1 to N-116; A-1 to C-115; A-1 to A-114; A-1 to D-113; A-1 to S-112; A-1 to Q-111; A-1 to P-110; A-1 to L-109; A-1 to M-108; A-1 to V-107; A-1 to M-106; A-1 to M-105; A-1 to D-104; A-1 to E-103; A-1 to P-102; A-1 to L-101; A-1 to G-100; A-1 to L-99; A-1 to T-98; A-1 to P-97; A-1 to Y-96; A-1 to F-95; A-1 to D-94; A-1 to Q-93; A-1 to F-92; A-1 to A-91; A-1 to K-90; A-1 to L-89; A-1 to A-88; A-1 to Q-87; A-1 to P-86; A-1 to S-85; A-1 to V-84; A-1 to D-83; A-1 to Q-82; A-1 to T-81; A-1 to R-80; A-1 to S-79; A-1 to Y-78; A-1 to L-77; A-1 to Q-76; A-1 to V-75; A-1 to M-74; A-1 to T-73; A-1 to S-72; A-1 to L-71; A-1 to A-70; A-1 to G-69; A-1 to E-68; A-1 to L-67; A-1 to E-66; A-1 to K-65; A-1 to Y-64; A-1 to I-63; A-1 to Y-62; A-1 to L-61; A-1 to V-60; A-1 to A-59; A-1 to F-58; A-1 to S-57; A-1 to S-56; A-1 to Y-55; A-1 to D-54; A-1 to T-53; A-1 to D-52; A-1 to V-51; A-1 to I-50; A-1 to R-49; A-1 to V-48; A-1 to D-47; A-1 to L-46; A-1 to Y-45; A-1 to G-44; A-1 to L-43; A-1 to A-42; A-1 to P-41; A-1 to V-40; A-1 to R-39; A-1 to F-38; A-1 to H-37; A-1 to G-36; A-1 to E-35; A-1 to S-34; A-1 to G-33; A-1 to V-32; A-1 to K-31; A-1 to L-30; A-1 to Y-29; A-1 to E-28; A-1 to A-27; A-1 to D-26; A-1 to V-25; A-1 to Q-24; A-1 to N-23; A-1 to C-22; A-1 to G-21; A-1 to D-20; A-1 to A-19; A-1 to G-18; A-1 to P-17; A-1 to F-16; A-1 to E-15; A-1 to M-14; A-1 to H-13; A-1 to V-12; A-1 to H-11; A-1 to L-10; A-1 to G-9; A-1 to G-8; or A-1 to E-7 of SEQ ID NO:201 (figure 1). Polypeptides encoded by these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that these bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Based on the sequence similarity to lipocalin of *Bufo marinus*, and the prostaglandin D synthase and cpl-1 proteins of *Xenopus laevis*, translation product of this gene is expected to share at least some biological activities with lipocalin motif-containing proteins, and specifically lipocalin, cpl-1, and prostaglandin D synthase proteins. Such activities are known in the art, some of which are described elsewhere herein.

Specifically, polynucleotides and polypeptides of the invention are also useful for modulating the differentiation of normal and malignant cells, binding to and activating small lipophilic molecules (e.g., retinal, retinoic acid, D/L thyroxine, etc.), modulating the synthesis of prostaglandin D, hormones, etc., and modulating the proliferation and/or dedifferentiation of cancer and neoplastic cells, particularly adenocarcinoma. Polynucleotides and polypeptides of the invention may represent a diagnostic marker for colon adenocarcinoma, and adenocarcinoma in general. The full-length protein should be a secreted protein, based upon homology to the lipocalin family.

Therefore, it is secreted into serum, urine, or feces and thus the levels is assayable from patient samples. Assuming specific expression levels are reflective of the presence of adenocarcinoma, this would provide a convenient diagnostic for early detection. In addition, expression of this gene product may also be linked to the progression of the disease, and therefore may itself actually represent a therapeutic or therapeutic target for the treatment of cancer. Therefore, based upon the tissue distribution of this protein in adenocarcinoma cells and tissues, antagonists directed against this protein is useful in blocking the activity of this protein. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene.

Also provided is a kit for detecting tumors in which expression of this protein occurs. Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, lymph, urine, seminal fluid, or feces and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the

antibody is bound to a solid support and the bodily fluid is serum. The above
embodiments, as well as other treatments and diagnostic tests (kits and methods), are
more particularly described elsewhere herein. Polynucleotides and polypeptides of the
invention may play an important role in the pathogenesis of human cancers and
5 cellular transformation, particularly those of the gastrointestinal, endocrine, and
immune systems, and specifically of colon adenocarcinoma, cervical adenocarcinoma,
and blood cells. Polynucleotides and polypeptides of the invention may also be
involved in the pathogenesis of developmental abnormalities based upon its potential
effects on proliferation and differentiation of cells and tissue cell types. Due to the
10 potential proliferating and differentiating activity of said polynucleotides and
polypeptides, the invention is useful as a therapeutic agent in inducing tissue
regeneration, for treating inflammatory conditions (e.g., inflammatory bowel
syndrome, diverticulitis, etc.). Moreover, the invention is useful in modulating the
immune response to aberrant polypeptides, as may exist in rapidly proliferating cells
15 and tissue cell types, particularly in adenocarcinoma cells, and other cancers.

This gene is expressed primarily in colon adenocarcinoma, cervical
adenocarcinoma, and cell line HeLa S3.

Therefore, polynucleotides and polypeptides of the invention are useful as
reagents for differential identification of the tissue(s) or cell type(s) present in a
20 biological sample and for diagnosis of diseases and conditions which include but are
not limited to: proliferative diseases and/or disorders, particularly adenocarcinomas.
Similarly, polypeptides and antibodies directed to these polypeptides are useful in
providing immunological probes for differential identification of the tissue(s) or cell
type(s). For a number of disorders of the above tissues or cells, particularly of the
25 gastrointestinal, endocrine, and immune systems, expression of this gene at
significantly higher or lower levels is routinely detected in certain tissues or cell types
(e.g., gastrointestinal, reproductive, endocrine, immune, and cancerous and wounded
tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal
fluid) or another tissue or sample taken from an individual having such a disorder,
30 relative to the standard gene expression level, i.e., the expression level in healthy
tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 108 as residues: Ser-66 to Ser-72, Pro-104 to Pro-110 (amino acid residues Ser-79 to Ser-85, Pro-117 to 123 of SEQ ID NO:201).

Polynucleotides encoding said polypeptides are also encompassed by the invention as are antibodies that bind said epitopes, domains, or other polypeptides of the invention.

The tissue distribution in colon adenocarcinoma indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "infectious disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses).

Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous Disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's Disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The protein product of this gene is thought to be involved in allergy and Th2 mediated responses. Therefore, antagonists of this protein is useful therapeutically for the treatment, detection, and/or

prevention of allergic responses, inhibiting eosinophil and basophil activation and release of mediators, and toxic shock syndromes.

Alternatively, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA).

Alternatively, this gene product is involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. In addition, other lipocalin family members, specifically cpl1, have been associated with playing a key role in early embryonic development. Through homology, it is expected that polypeptides and polynucleotides of the present invention may also play similar roles. Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and is useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases.

The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological

activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence
10 would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 556 of SEQ ID NO:37, b is an integer of 15 to 570, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 28

The gene encoding the disclosed cDNA is believed to reside on chromosome 6. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 6.

20 In specific embodiments, polypeptides of the invention comprise, or alternatively consists of, the following amino acid sequence:
PRVRNRKRRLSAVPAGGGEAAVGS LGCVSPVMEPGPTAAQRRCSLPPWLPLG
LLLWSGLALGALPFGSSPHRVFHDLLSEQQLLEVEDLSLSLLQGGGLGPLSLPP
DLPDLDPECRELLLD FANSSAELTGCLVRSARPVRLCQTCYPLFQQV VSKMD
25 NISRAAGNTSESQSCARSLLMADRMQIVVILSEFFNTTWQEANCANCLTNNSE
ELSNSTVYFLKSI (SEQ ID NO: 205) and
MEPGPTAAQRRCSLPPWLPLG LLLWSGLALGALPFGSSPHRVFHDLLSEQQLL
EVEDLSLSLLQGGGLGPLSLPPDLPDLDPECRELLLD FANSSAELTGCLVRSAR
PVRLCQTCYPLFQQV VSKMDNISRAAGNTSESQSCARSLLMADRMQIVVILSE
30 FFNTTWQEANCANCLTNNSEELSNSTVYFLKSI (SEQ ID NO:). Moreover,
fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or

99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in osteoclastoma, T-cell, pineal gland, adipose tissue, placenta, dendritic cells, fetal tissue (e.g., heart) and to a lesser extent in many other tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to: immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 109 as residues: Glu-2 to Ser-13, Pro-75 to Leu-80. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution in immune cells (e.g., T-cells) indicates the protein product of this clone is useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved

in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3215 of SEQ ID NO:38, b is an integer of 15 to 3229, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 29

The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 3-19 of the amino acid sequence referenced in
5 Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 20-75 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

This gene is expressed primarily in parathyroid tumor, brain, placenta, ovarian
10 cancer, healing groin wound, osteoclastoma and to a lesser extent in many other tissues.

Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include but are not limited to:
15 ovarian cancer, neurological disorders, and/or parathyroid cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the female reproductive system, endocrine and exocrine system, expression of this gene at
20 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., ovaries, cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having
25 the disorder.

The tissue distribution in parathyroid tumor and ovarian cancer tissue indicates the protein product of this clone would be useful for the detection, treatment, and/or prevention of various endocrine and reproductive disorders and cancers. Representative uses are described in the "Biological Activity", "Hyperproliferative
30 Disorders", and "Binding Activity" sections below, in Example 11, 17, 18, 19, 20 and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of Addison's disease, Cushing's Syndrome, and disorders and/or

cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 497 of SEQ ID NO:39, b is an integer of 15 to 511, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

20 FEATURES OF PROTEIN ENCODED BY GENE NO: 30

The translation product of this gene shares sequence homology with apolipoprotein A-IV (see, e.g., Genbank Accession Nos. emb|CAA11020.1| (AJ222966) and gb|AAA35379.1|; all references available through these accessions are hereby incorporated in their entirety by reference herein). (Genbank Accession Nos. emb CAA11020.1 polypeptide sequence:

MFLKAVVLSLALVAVTGARAEVNADQVATVMWDYFSQLGSSNAKKAVEHLQ
 KSELTQQNLTLFQDKLGEVNTYTEDLQKKLVFPATELHERLTKDSEKLKEEIR
 RELEELRARLLPHATEVSQKIGDNVRELQQRLLGPFTGGLRTQVNTQVQQQLQR
 QLKPYAERMESVLRQNIRNLEASVAPYADEFKAKIDQNVEELKGSLLTPYAEEL
 KAKIDQNVEELRRSLAPYAQDVQEKLNHQLEGLAFQMKKQAEELKAKISAN
 ADELRLQKLVPVAENVHGHKGNTEGLQKSLLRLSHLDQQVEEFRLKVEPYG
 ETFNKALVQQVEDLRQKLGLAGDVEGHLSFLEKDLRDKVNTFFSTLKEEAS

QGQSQUALPAQEKAQAPLEG (SEQ ID NO: 206). Genbank Accession Nos. gb
AAA35379.1:

MFLKAVVLTALVAVAGARAEVSADQVATVMWDYFSQLSNNAKEAVEHLQ
KSELTQQLNALFQDKLGEVNTYAGDLQKKLVPFATELHERLAKDSEKLKEEI
5 GKELEELRARLLPHANEVSQKIGDNLRELQQRLEPYADQLRTQVNTQAEQLR
RQLDPLAQRMERVLRENADSLQASLRPHADELKAKIDQNV EELKGRLTPYAD
EFKVKIDQTVEELRRSLAPYAQDTQEKLNHQLEGLTFQMKKNAEELKARISA
SAEELRQRLAPLAEDVRGNLKGNT EQLQKSLAELGGHLDQQVEEFRRRVEPY
GENFNKALVQQMEQLRQKLGP HAGDVEGHLSFLEKDLRDKVNSFFSTFKEKE

10 SQDKTSLPELEQQQEQQQEQQQEQVQMLAPLES (SEQ ID NO: 207). Genbank
Accession No. gb AAA37214.1:

MFLKAAVLTALVAITGTRAEVTSQVANVVDYFTQLSNNAKEAVEQFQK
TDVTQQLSTLFQDKLGDASTYADGVHNKLVPFVVQLSGHLAKETERVKEEIK
KELEDLRDRMMPHANKVTQTFGENMQKLQEHLKPYAVDLQDQINTQTQEM
15 KLQLTPYIQRMQTTIKENVDNLHTSMMPLATNLKDKFNRNMEELKGHLTPRA
NELKATIDQNLEDLRRSLAPLTVGVQEKLNHQMEGLAFQMKKNAEELQTKV
SAKIDQLQKNLAPLVEDVQSKVKGNT EQLQKSLEDLNRQLEQQVEEFRRTVE
PMGEMFNKALVQQLEQFRQQLGPNSGEVESHL SFLEKSLREKVNSFMSTLEK
KGSPDQPQALPLPEQAQEQAQEQVQPKPLES (SEQ ID NO: 208).).

20 This invention relates to newly identified Apolipoprotein polynucleotides,
polypeptides encoded by such polynucleotides, the use of such polynucleotides and
polypeptides, as well as the production of such polynucleotides and polypeptides. The
polypeptide of the present invention has been putatively identified as a human
apolipoprotein A-IV homolog derived from a normal human liver cDNA library,
25 sometimes hereafter referred to as "Apolipoprotein A-IV-Like" and/or "ApoA-IV-L".
The invention also relates to inhibiting the action of such polypeptides.

Apolipoproteins are protein constituents of plasma lipid transport particles.
ApoA-IV is associated with triglyceride-rich lipoproteins and HDL, and also occurs in
a lipoprotein-free form. It has been proposed to play a role in reverse cholesterol
30 transport on the basis of in vitro properties. It has been demonstrated that apoA-IV
can bind to hepatocytes. Since it appears that the expression of our homolog, apoA-
IV-L, is liver-enriched, if not liver-specific, perhaps there is some "hand-off"

mechanism, whereby HDL/cholesterol is transported to the liver by apoA-IV and transferred to apoA-IV-L for elimination from the liver. Therefore, apoA-IV-L is intimately involved in cholesterol metabolism, cholesterol transport, and removal of cholesterol from the body. The ApoA-IV protein has also been attributed to
5 regulating food-intake (J Nutr. 1999 Aug;129(8):1503-6).

In transgenic mice that are expressing apoA-IV in the liver, it appears that apoA-IV can protect against atherosclerosis by a mechanism that does not involve an increase in HDL cholesterol concentration. Therefore, perhaps our homolog, apoA-IV-L can also provide protection against atherosclerosis.

10

Studies have demonstrated that dietary fat clearance is modulated by genetic variation in the apolipoprotein A-IV gene locus. For example, the A-IV-347Ser polymorphism is associated with the variability in low density lipoprotein (LDL)-cholesterol response to dietary therapy. A putative polymorphism has been
15 specifically identified within the present invention (a serine to isoleucine polymorphism at amino acid residue 258 of Figures 7A-B (amino acid residue 258 of SEQ ID NO: 212). Perhaps this possible polymorphism, or others as yet undetected in the gene locus for apoA-IV-L may likewise provide a diagnostic for altered lipid/cholesterol/bile metabolism.

20

Interestingly, other apolipoproteins, specifically apolipoprotein(a) ("apo(a)") is a recognized cardiovascular risk factor. Apo(a) is characterized by a high genetic polymorphism with at least 34 isoforms in plasma. Recent studies have shown that in atherothrombosis apo(a) polymorphism could play a role independent of Lp(a) levels. In particular, apo(a) phenotypes seem to have their highest predictive value for
25 coronary heart disease, when apo(a) isoforms are detected by high resolution phenotyping methods and when an adequate operative cut-off of apo(a) polymorphism is used. A strong association between apo(a) phenotypes and coronary heart disease has been also found in hypertensive, diabetic, and uremic patients. Moreover, apo(a) phenotypes seem to correlate well with the severity of coronary atherosclerosis and
30 the age of clinical onset of coronary heart disease. These studies suggest that apo(a) polymorphism may have a great clinical usefulness in a primary prevention setting, since apo(a) phenotypes could be used together with Lp(a) levels as strong genetic

predictors of atherothrombosis. The analysis of apo(a) polymorphism appears to be particularly useful in healthy subjects with a family history of atherothrombotic diseases, in patients with diseases at high cardiovascular risk (diabetes, hypertension, hypercholesterolemia) and in subjects with conditions modifying Lp(a) levels
5 (Cardiologia. 1999 Apr;44(4):347-54, and Am J Cardiol. 1999 May 13;83(9B):3F-12F). Thus, it is anticipated that at the present apolipoprotein A-IV-like protein, and/or polymorphisms thereof, may portray similar clinical phenotypes, whose expression levels may also serve as a diagnostic for cardiovascular diseases and/or disorders, if not also for liver diseases and/or disorders.

10 The polypeptide of the present invention has been putatively identified as a member of the apolipoprotein family and has been termed Apolipoprotein A-IV-Like protein ("ApoA-IV-L"). This identification has been made as a result of amino acid sequence homology to the apolipoprotein A-IV of *Sus scrofa* (emb|CAA11020.1), the human apolipoprotein A-IV (gb|AAA51744.1), and the mouse apolipoprotein A-IV
15 (gb|AAA37214.1).

Figures 7A-B show the nucleotide (SEQ ID NO: 40) and deduced amino acid sequence (SEQ ID NO: 212) of ApoA-IV-L. Predicted amino acids from about 1 to about 23 constitute the predicted signal sequence (amino acid residues from about 1 to about 23 in SEQ ID NO: 212) and are represented by the underlined amino acid
20 regions; and nucleic acid residues from about 781 to about 885 (nucleic acid residues from about 781 to about 885 in SEQ ID NO:212 which constitutes the putative polymorphism domain as is represented by the double underlined nucleic acids; and amino acid 258 which constitutes a putative Serine to Isoleucine polymorphism (amino acid residue 258 in SEQ ID NO:212 and is represented by the bold amino acid.

25 Figure 8A-8B shows the regions of similarity between the amino acid sequences of the Apolipoprotein A-IV-Like (ApoA-IV-L) protein (SEQ ID NO:212) the apolipoprotein A-IV of *Sus scrofa* (SEQ ID NO: 206), the human apolipoprotein A-IV (SEQ ID NO: 207), and the mouse apolipoprotein A-IV (SEQ ID NO: 208).

Figure 9 shows an analysis of the Apolipoprotein A-IV-Like (ApoA-IV-L)
30 amino acid sequence. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown.

A polynucleotide encoding a polypeptide of the present invention is obtained from human normal liver, hepatoma, and pancreas tumor tissues. The polynucleotide of this invention was discovered in a human normal liver cDNA library. As shown in Figures 7A-B and Figure 8, ApoA-IV-L has strong conservation between other members of the apolipoprotein A-IV family. The polynucleotide contains an open reading frame encoding the full-length apolipoprotein A-IV polypeptide of 366 amino acids, and a predicted molecular weight of 41.237 kilodaltons. ApoA-IV-L exhibits a high degree of homology at the amino acid level to the the apolipoprotein A-IV of Sus scrofa, the human apolipoprotein A-IV, and the mouse apolipoprotein A-IV (as shown in Figure 8).

The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding the ApoA-IV-L polypeptide having the amino acid sequence shown in Figures 7A-B (SEQ ID NO: 212). The nucleotide sequence shown in Figures 7A-B (SEQ ID NO: 40) was obtained by sequencing a cDNA gene (HLDRR08), which was deposited on September 27, 1999 at the American Type Culture Collection, and given Accession Number PTA-796. The deposited gene (HLDRR08) is inserted in the pCMV Sport 3.0 plasmid (Life Technologies, Rockville, MD) using the SalI/NotI restriction endonuclease cleavage sites.

The present invention is further directed to fragments of the isolated nucleic acid molecules described herein. By a fragment of an isolated DNA molecule having the nucleotide sequence of the deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 40 is intended DNA fragments at least about 15nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt in length which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 50-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of the deposited cDNA or as shown in SEQ ID NO: 40. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of the deposited cDNA or the nucleotide sequence as shown in SEQ ID NO: 40. In this context "about" includes the particularly recited size, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Representative examples of ApoA-IV-L polynucleotide fragments of the invention include, for example, fragments that comprise, or

Alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, from about 501 to about 550, from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, from about 801 to about 850, from about 851 to about 900, from about 901 to about 950, from about 951 to about 1000, from about 1001 to about 1050, from about 1051 to about 1100, from about 1101 to about 1150, from about 1151 to about 1200, from about 1201 to about 1250, from about 1251 to about 1300, from about 1301 to about 1350, from about 1351 to about 1393, from about 64 to about 129, from about 67 to about 1161, and from about 130 to about 1161 of SEQ ID NO: 40 (Figures 7A-B), or the complementary strand thereto, or the cDNA contained in the deposited gene. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Alternatively, consisting of, the predicted mature apolipoprotein A-IV-L (amino acid residues from about 24 to about 366 in Figures 7A-B (amino acids from about 24 to about 366 in SEQ ID NO: 212); the full-length apolipoprotein A-IV-L (amino acid residues from about 1 to about 366 in Figures 7A-B (amino acid residues from about 1 to about 366 in SEQ ID NO: 212); the full-length apolipoprotein A-IV-L minus the start methionin (amino acid residues from about 2 to about 366 in Figures 7A-B (amino acid residues from about 2 to about 366 in SEQ ID NO: 212). In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

Alternatively, consist of, the putative polymorphic domain, and specifically polynucleotide fragments having a sequence from about nucleotide 825 to about 846, from about 822 to about 849, from about 820 to about 852, from about 817 to about 855, from about 814 to about 858, from about 811 to about 861, from about 808 to about 864, from about 805 to about 867, from about 802 to about 870, from about 799

to about 873, from about 796 to about 876, from about 793 to about 879, from about 790 to about 882, from about 787 to about 885, from about 784 to about 888, and from about 781 to about 891 of SEQ ID NO: 40 (Figures 7A-B). In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, 5 or 1) nucleotides, at either terminus or at both termini, and potentially as many as 10, 20, 30, 40, 50, or 100 nucleotides, at either terminus or at both termini. Such polynucleotide fragments could be used diagnostically to identify individuals, organisms, and/or cells at risk for metabolic, liver, and cardiovascular diseases and/or disorders through the application of such fragments in modern RFLP and SLP polymorphism analysis. The methodology of such an analysis would readily be 10 apparent to the skilled artisan. Though a few examples are referenced in Methods Mol Biol. 1998;110:1-34, J Clin Lab Anal. 1999;13(5):205-208, and Am. J. Hum. Genet. 44:388-396.

In additional embodiments, the polynucleotides of the invention encode 15 functional attributes of ApoA-IV-L. Preferred embodiments of the invention in this regard include fragments that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta 20 amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions of ApoA-IV-L.

The data representing the structural or functional attributes of ApoA-IV-L set forth in Figure 9 and/or Table 9, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred 25 embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 9 can be used to determine regions of ApoA-IV-L which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an 30 environment in which antigen recognition may occur in the process of initiation of an immune response.

Certain preferred regions in these regards are set out in Figure 9, but may, as shown in Table 9, be represented or identified by using tabular representations of the data presented in Figure 9. The DNA*STAR computer algorithm used to generate Figure 9 (set on the original default parameters) was used to present the data in Figure 9 in a tabular format (See Table 9). The tabular format of the data in Figure 9 is used to easily determine specific boundaries of a preferred region.

The above-mentioned preferred regions set out in Figure 9 and in Table 9 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in Figure 7A-7B. As set out in Figure 9 and in Table 9, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and Hopp-Woods hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions.

Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, etc.) may still be retained. For example, the ability of shortened ApoA-IV-L muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that an ApoA-IV-L mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six ApoA-IV-L amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues deleted from the amino terminus of the ApoA-IV-L amino acid sequence shown in Figure 7A-7B, up to the serine residue at position number 361 and polynucleotides encoding such polypeptides. In particular, the present invention

provides polypeptides comprising the amino acid sequence of residues n1-366 of Figure 7A-7B, where n1 is an integer from 2 to 361 corresponding to the position of the amino acid residue in Figure 7A-7B (which is identical to the sequence shown as SEQ ID NO: 212).

5 In another embodiment, N-terminal deletions of the ApoA-IV-L polypeptide can be described by the general formula n2-361, where n2 is a number from 2 to 361, corresponding to the position of amino acid identified in Figure 7A-7B. N-terminal deletions of the ApoA-IV-L polypeptide of the invention shown as SEQ ID NO: 212 include polypeptides comprising the amino acid sequence of residues: N-terminal
 10 deletions of the ApoA-IV-L polypeptide of the invention shown as SEQ ID NO: 212 include polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues: A-2 to P-366; S-3 to P-366; M-4 to P-366; A-5 to P-366; A-6 to P-366; V-7 to P-366; L-8 to P-366; T-9 to P-366; W-10 to P-366; A-11 to P-366; L-12 to P-366; A-13 to P-366; L-14 to P-366; L-15 to P-366; S-16 to P-366; A-17 to P-366;
 15 F-18 to P-366; S-19 to P-366; A-20 to P-366; T-21 to P-366; Q-22 to P-366; A-23 to P-366; R-24 to P-366; K-25 to P-366; G-26 to P-366; F-27 to P-366; W-28 to P-366; D-29 to P-366; Y-30 to P-366; F-31 to P-366; S-32 to P-366; Q-33 to P-366; T-34 to P-366; S-35 to P-366; G-36 to P-366; D-37 to P-366; K-38 to P-366; G-39 to P-366; R-40 to P-366; V-41 to P-366; E-42 to P-366; Q-43 to P-366; I-44 to P-366; H-45 to P-
 20 366; Q-46 to P-366; Q-47 to P-366; K-48 to P-366; M-49 to P-366; A-50 to P-366; R-51 to P-366; E-52 to P-366; P-53 to P-366; A-54 to P-366; T-55 to P-366; L-56 to P-366; K-57 to P-366; D-58 to P-366; S-59 to P-366; L-60 to P-366; E-61 to P-366; Q-62 to P-366; D-63 to P-366; L-64 to P-366; N-65 to P-366; N-66 to P-366; M-67 to P-366; N-68 to P-366; K-69 to P-366; F-70 to P-366; L-71 to P-366; E-72 to P-366; K-
 25 73 to P-366; L-74 to P-366; R-75 to P-366; P-76 to P-366; L-77 to P-366; S-78 to P-366; G-79 to P-366; S-80 to P-366; E-81 to P-366; A-82 to P-366; P-83 to P-366; R-84 to P-366; L-85 to P-366; P-86 to P-366; Q-87 to P-366; D-88 to P-366; P-89 to P-366; V-90 to P-366; G-91 to P-366; M-92 to P-366; R-93 to P-366; R-94 to P-366; Q-95 to P-366; L-96 to P-366; Q-97 to P-366; E-98 to P-366; E-99 to P-366; L-100 to P-366;
 30 E-101 to P-366; E-102 to P-366; V-103 to P-366; K-104 to P-366; A-105 to P-366; R-106 to P-366; L-107 to P-366; Q-108 to P-366; P-109 to P-366; Y-110 to P-366; M-111 to P-366; A-112 to P-366; E-113 to P-366; A-114 to P-366; H-115 to P-366; E-

116 to P-366; L-117 to P-366; V-118 to P-366; G-119 to P-366; W-120 to P-366; N-121 to P-366; L-122 to P-366; E-123 to P-366; G-124 to P-366; L-125 to P-366; R-126 to P-366; Q-127 to P-366; Q-128 to P-366; L-129 to P-366; K-130 to P-366; P-131 to P-366; Y-132 to P-366; T-133 to P-366; M-134 to P-366; D-135 to P-366; L-136 to P-366; M-137 to P-366; E-138 to P-366; Q-139 to P-366; V-140 to P-366; A-141 to P-366; L-142 to P-366; R-143 to P-366; V-144 to P-366; Q-145 to P-366; E-146 to P-366; L-147 to P-366; Q-148 to P-366; E-149 to P-366; Q-150 to P-366; L-151 to P-366; R-152 to P-366; V-153 to P-366; V-154 to P-366; G-155 to P-366; E-156 to P-366; D-157 to P-366; T-158 to P-366; K-159 to P-366; A-160 to P-366; Q-161 to P-366; L-162 to P-366; L-163 to P-366; G-164 to P-366; G-165 to P-366; V-166 to P-366; D-167 to P-366; E-168 to P-366; A-169 to P-366; W-170 to P-366; A-171 to P-366; L-172 to P-366; L-173 to P-366; Q-174 to P-366; G-175 to P-366; L-176 to P-366; Q-177 to P-366; S-178 to P-366; R-179 to P-366; V-180 to P-366; V-181 to P-366; H-182 to P-366; H-183 to P-366; T-184 to P-366; G-185 to P-366; R-186 to P-366; F-187 to P-366; K-188 to P-366; E-189 to P-366; L-190 to P-366; F-191 to P-366; H-192 to P-366; P-193 to P-366; Y-194 to P-366; A-195 to P-366; E-196 to P-366; S-197 to P-366; L-198 to P-366; V-199 to P-366; S-200 to P-366; G-201 to P-366; I-202 to P-366; G-203 to P-366; R-204 to P-366; H-205 to P-366; V-206 to P-366; Q-207 to P-366; E-208 to P-366; L-209 to P-366; H-210 to P-366; R-211 to P-366; S-212 to P-366; V-213 to P-366; A-214 to P-366; P-215 to P-366; H-216 to P-366; A-217 to P-366; P-218 to P-366; A-219 to P-366; S-220 to P-366; P-221 to P-366; A-222 to P-366; R-223 to P-366; L-224 to P-366; S-225 to P-366; R-226 to P-366; C-227 to P-366; V-228 to P-366; Q-229 to P-366; V-230 to P-366; L-231 to P-366; S-232 to P-366; R-233 to P-366; K-234 to P-366; L-235 to P-366; T-236 to P-366; L-237 to P-366; K-238 to P-366; A-239 to P-366; K-240 to P-366; A-241 to P-366; L-242 to P-366; H-243 to P-366; A-244 to P-366; R-245 to P-366; I-246 to P-366; Q-247 to P-366; Q-248 to P-366; N-249 to P-366; L-250 to P-366; D-251 to P-366; Q-252 to P-366; L-253 to P-366; R-254 to P-366; E-255 to P-366; E-256 to P-366; L-257 to P-366; I-258 to P-366; R-259 to P-366; A-260 to P-366; F-261 to P-366; A-262 to P-366; G-263 to P-366; T-264 to P-366; G-265 to P-366; T-266 to P-366; E-267 to P-366; E-268 to P-366; G-269 to P-366; A-270 to P-366; G-271 to P-366; P-272 to P-366; D-273 to P-366; P-274 to P-366; Q-275 to P-366; M-276 to P-366; L-277 to P-366; S-278 to P-

366; E-279 to P-366; E-280 to P-366; V-281 to P-366; R-282 to P-366; Q-283 to P-366; R-284 to P-366; L-285 to P-366; Q-286 to P-366; A-287 to P-366; F-288 to P-366; R-289 to P-366; Q-290 to P-366; D-291 to P-366; T-292 to P-366; Y-293 to P-366; L-294 to P-366; Q-295 to P-366; I-296 to P-366; A-297 to P-366; A-298 to P-366; F-299 to P-366; T-300 to P-366; R-301 to P-366; A-302 to P-366; I-303 to P-366; D-304 to P-366; Q-305 to P-366; E-306 to P-366; T-307 to P-366; E-308 to P-366; E-309 to P-366; V-310 to P-366; Q-311 to P-366; Q-312 to P-366; Q-313 to P-366; L-314 to P-366; A-315 to P-366; P-316 to P-366; P-317 to P-366; P-318 to P-366; P-319 to P-366; G-320 to P-366; H-321 to P-366; S-322 to P-366; A-323 to P-366; F-324 to P-366; A-325 to P-366; P-326 to P-366; E-327 to P-366; F-328 to P-366; Q-329 to P-366; Q-330 to P-366; T-331 to P-366; D-332 to P-366; S-333 to P-366; G-334 to P-366; K-335 to P-366; V-336 to P-366; L-337 to P-366; S-338 to P-366; K-339 to P-366; L-340 to P-366; Q-341 to P-366; A-342 to P-366; R-343 to P-366; L-344 to P-366; D-345 to P-366; D-346 to P-366; L-347 to P-366; W-348 to P-366; E-349 to P-366; D-350 to P-366; I-351 to P-366; T-352 to P-366; H-353 to P-366; S-354 to P-366; L-355 to P-366; H-356 to P-366; D-357 to P-366; Q-358 to P-366; G-359 to P-366; H-360 to P-366; or S-361 to P-366; of SEQ ID NO: 212. Polypeptides encoded by these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that these bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities (e.g., ability to transport lipids, cholesterol transport, metabolize lipoprotein, etc.), ability to multimerize, and the ability to activate lecithin cholesterol acyltransferase may still be retained. For example the ability of the shortened ApoA-IV-L mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the

polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that an ApoA-IV-L mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six ApoA-IV-L amino acid residues may often evoke an immune response.

Preferred polypeptides of the invention comprise the following amino acid sequence:

MASMAAVLTWALALLSAFSATQARKGFWDYFSQTSGDKGRVEQIHQQKMA
REPATLKDSLEQDLNNMNKFLEKLRPLSGSEAPRLPQDPVGMRRQLQEELEE
VKARLQPYMAEAHELVGWNLEGLRQQKPYTMDLMEQVALRVQELQEQLR
VVGEDTKAQLLGGVDEAWALLQGLQSRVVHHTGRFKELFHPYAESLVSGIG
RHVQELHRSVAPHAPASPARLSRCVQVLSRKLTAKALHARIQQNLDQLRE
ELIRAFAGTGTEEGAGPDPQMLSEEVQRQLQAFRQDTYLQIAAFTRAIDQETE
EVQQQLAPPPPGHSAFAPEFQQTDSGKVL SKLQARLDDLWEDITHSLHDQGH
SHLGDP (SEQ ID NO: 155). Polynucleotides encoding these polypeptides are also

encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof are encompassed by the invention. Antibodies that these bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In another embodiment, the polypeptide sequence illustrated in Table I for this gene (SEQ ID NO:96) represents a potential alternative secreted form of the protein. Based upon the location of the start methionine of this polypeptide sequence with respect to the start methionine of the sequence shown in Figures 7A-B (SEQ ID NO: 212), it is unclear which start methionine the cell will utilize during expression.

Thus, both SEQ ID NO: 212 and SEQ ID NO:96 are contemplated by the present invention.

Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the ApoA-IV-L polypeptide shown in Figure 7A-7B, up to the valine residue at position number 7, and polynucleotides encoding such polypeptides. In particular, the present invention provides polypeptides comprising the amino acid sequence of residues 1-m1 of Figure 7A-7B, where m1 is an integer from 7 to 336 corresponding to the position of the amino acid residue in Figure 7A-7B.

Moreover, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, the amino acid sequence of C-terminal deletions of the ApoA-IV-L polypeptide of the invention shown as SEQ ID NO: 212 (Figures 7A-B) include polypeptides comprising, or alternatively consisting of the amino acid sequence of residues: M-1 to D-365; M-1 to G-364; M-1 to L-363; M-1 to H-362; M-1 to S-361; M-1 to H-360; M-1 to G-359; M-1 to Q-358; M-1 to D-357; M-1 to H-356; M-1 to L-355; M-1 to S-354; M-1 to H-353; M-1 to T-352; M-1 to I-351; M-1 to D-350; M-1 to E-349; M-1 to W-348; M-1 to L-347; M-1 to D-346; M-1 to D-345; M-1 to L-344; M-1 to R-343; M-1 to A-342; M-1 to Q-341; M-1 to L-340; M-1 to K-339; M-1 to S-338; M-1 to L-337; M-1 to V-336; M-1 to K-335; M-1 to G-334; M-1 to S-333; M-1 to D-332; M-1 to T-331; M-1 to Q-330; M-1 to Q-329; M-1 to F-328; M-1 to E-327; M-1 to P-326; M-1 to A-325; M-1 to F-324; M-1 to A-323; M-1 to S-322; M-1 to H-321; M-1 to G-320; M-1 to P-319; M-1 to P-318; M-1 to P-317; M-1 to P-316; M-1 to A-315; M-1 to L-314; M-1 to Q-313; M-1 to Q-312; M-1 to Q-311; M-1 to V-310; M-1 to E-309; M-1 to E-308; M-1 to T-307; M-1 to E-306; M-1 to Q-305; M-1 to D-304; M-1 to I-303; M-1 to A-302; M-1 to R-301; M-1 to T-300; M-1 to F-299; M-1 to A-298; M-1 to A-297; M-1 to I-296; M-1 to Q-295; M-1 to L-294; M-1 to Y-293; M-1 to T-292; M-1 to D-291; M-1 to Q-290; M-1 to R-289; M-1 to F-288; M-1 to A-287; M-1 to Q-286; M-1 to L-285; M-1 to R-284; M-1 to Q-283; M-1 to R-282; M-1 to V-281; M-1 to E-280; M-1 to E-279; M-1 to S-278; M-1 to L-277; M-1 to M-276; M-1 to Q-275; M-1 to P-274; M-1 to D-273; M-1 to P-272; M-1 to G-271; M-1 to A-270; M-1 to G-269; M-1 to E-268; M-1 to E-267; M-1 to T-266; M-1 to G-265; M-1 to T-264; M-1 to G-263; M-1 to A-262; M-1 to F-261; M-1 to A-260; M-1 to R-

259; M-1 to I-258; M-1 to L-257; M-1 to E-256; M-1 to E-255; M-1 to R-254; M-1 to L-253; M-1 to Q-252; M-1 to D-251; M-1 to L-250; M-1 to N-249; M-1 to Q-248; M-1 to Q-247; M-1 to I-246; M-1 to R-245; M-1 to A-244; M-1 to H-243; M-1 to L-242; M-1 to A-241; M-1 to K-240; M-1 to A-239; M-1 to K-238; M-1 to L-237; M-1 to T-236; M-1 to L-235; M-1 to K-234; M-1 to R-233; M-1 to S-232; M-1 to L-231; M-1 to V-230; M-1 to Q-229; M-1 to V-228; M-1 to C-227; M-1 to R-226; M-1 to S-225; M-1 to L-224; M-1 to R-223; M-1 to A-222; M-1 to P-221; M-1 to S-220; M-1 to A-219; M-1 to P-218; M-1 to A-217; M-1 to H-216; M-1 to P-215; M-1 to A-214; M-1 to V-213; M-1 to S-212; M-1 to R-211; M-1 to H-210; M-1 to L-209; M-1 to E-208; M-1 to Q-207; M-1 to V-206; M-1 to H-205; M-1 to R-204; M-1 to G-203; M-1 to I-202; M-1 to G-201; M-1 to S-200; M-1 to V-199; M-1 to L-198; M-1 to S-197; M-1 to E-196; M-1 to A-195; M-1 to Y-194; M-1 to P-193; M-1 to H-192; M-1 to F-191; M-1 to L-190; M-1 to E-189; M-1 to K-188; M-1 to F-187; M-1 to R-186; M-1 to G-185; M-1 to T-184; M-1 to H-183; M-1 to H-182; M-1 to V-181; M-1 to V-180; M-1 to R-179; M-1 to S-178; M-1 to Q-177; M-1 to L-176; M-1 to G-175; M-1 to Q-174; M-1 to L-173; M-1 to L-172; M-1 to A-171; M-1 to W-170; M-1 to A-169; M-1 to E-168; M-1 to D-167; M-1 to V-166; M-1 to G-165; M-1 to G-164; M-1 to L-163; M-1 to L-162; M-1 to Q-161; M-1 to A-160; M-1 to K-159; M-1 to T-158; M-1 to D-157; M-1 to E-156; M-1 to G-155; M-1 to V-154; M-1 to V-153; M-1 to R-152; M-1 to L-151; M-1 to Q-150; M-1 to E-149; M-1 to Q-148; M-1 to L-147; M-1 to E-146; M-1 to Q-145; M-1 to V-144; M-1 to R-143; M-1 to L-142; M-1 to A-141; M-1 to V-140; M-1 to Q-139; M-1 to E-138; M-1 to M-137; M-1 to L-136; M-1 to D-135; M-1 to M-134; M-1 to T-133; M-1 to Y-132; M-1 to P-131; M-1 to K-130; M-1 to L-129; M-1 to Q-128; M-1 to Q-127; M-1 to R-126; M-1 to L-125; M-1 to G-124; M-1 to E-123; M-1 to L-122; M-1 to N-121; M-1 to W-120; M-1 to G-119; M-1 to V-118; M-1 to L-117; M-1 to E-116; M-1 to H-115; M-1 to A-114; M-1 to E-113; M-1 to A-112; M-1 to M-111; M-1 to Y-110; M-1 to P-109; M-1 to Q-108; M-1 to L-107; M-1 to R-106; M-1 to A-105; M-1 to K-104; M-1 to V-103; M-1 to E-102; M-1 to E-101; M-1 to L-100; M-1 to E-99; M-1 to E-98; M-1 to Q-97; M-1 to L-96; M-1 to Q-95; M-1 to R-94; M-1 to R-93; M-1 to M-92; M-1 to G-91; M-1 to V-90; M-1 to P-89; M-1 to D-88; M-1 to Q-87; M-1 to P-86; M-1 to L-85; M-1 to R-84; M-1 to P-83; M-1 to A-82; M-1 to E-81; M-1 to S-80; M-1 to G-79; M-1 to S-78; M-1 to L-77; M-1 to P-76; M-1 to R-75; M-1 to L-

74; M-1 to K-73; M-1 to E-72; M-1 to L-71; M-1 to F-70; M-1 to K-69; M-1 to N-68; M-1 to M-67; M-1 to N-66; M-1 to N-65; M-1 to L-64; M-1 to D-63; M-1 to Q-62; M-1 to E-61; M-1 to L-60; M-1 to S-59; M-1 to D-58; M-1 to K-57; M-1 to L-56; M-1 to T-55; M-1 to A-54; M-1 to P-53; M-1 to E-52; M-1 to R-51; M-1 to A-50; M-1 to M-49; M-1 to K-48; M-1 to Q-47; M-1 to Q-46; M-1 to H-45; M-1 to I-44; M-1 to Q-43; M-1 to E-42; M-1 to V-41; M-1 to R-40; M-1 to G-39; M-1 to K-38; M-1 to D-37; M-1 to G-36; M-1 to S-35; M-1 to T-34; M-1 to Q-33; M-1 to S-32; M-1 to F-31; M-1 to Y-30; M-1 to D-29; M-1 to W-28; M-1 to F-27; M-1 to G-26; M-1 to K-25; M-1 to R-24; M-1 to A-23; M-1 to Q-22; M-1 to T-21; M-1 to A-20; M-1 to S-19; M-1 to F-18; M-1 to A-17; M-1 to S-16; M-1 to L-15; M-1 to L-14; M-1 to A-13; M-1 to L-12; M-1 to A-11; M-1 to W-10; M-1 to T-9; M-1 to L-8; M-1 to V-7; and M-1 to A-6; of SEQ ID NO: 212. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

Moreover, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, the following amino acid sequences of C-terminal deletions of the mature ApoA-IV-L polypeptide of the invention shown as SEQ ID NO: 212 (Figures 7A-B):

R-24 to D-365; R-24 to G-364; R-24 to L-363; R-24 to H-362; R-24 to S-361; R-24 to H-360; R-24 to G-359; R-24 to Q-358; R-24 to D-357; R-24 to H-356; R-24 to L-355; R-24 to S-354; R-24 to H-353; R-24 to T-352; R-24 to I-351; R-24 to D-350; R-24 to E-349; R-24 to W-348; R-24 to L-347; R-24 to D-346; R-24 to D-345; R-24 to L-344; R-24 to R-343; R-24 to A-342; R-24 to Q-341; R-24 to L-340; R-24 to K-339; R-24 to S-338; R-24 to L-337; R-24 to V-336; R-24 to K-335; R-24 to G-334; R-24 to S-333; R-24 to D-332; R-24 to T-331; R-24 to Q-330; R-24 to Q-329; R-24 to F-328; R-24 to E-327; R-24 to P-326; R-24 to A-325; R-24 to F-324; R-24 to A-323; R-24 to S-322; R-24 to H-321; R-24 to G-320; R-24 to P-319; R-24 to P-318; R-24 to P-317; R-24 to P-316; R-24 to A-315; R-24 to L-314; R-24 to Q-313; R-24 to Q-312; R-24 to Q-311; R-24 to V-310; R-24 to E-309; R-24 to E-308; R-24 to T-307; R-24 to E-306; R-24 to Q-305; R-24 to D-304; R-24 to I-303; R-24 to A-302; R-24 to R-301; R-24 to T-300; R-24 to F-299; R-24 to A-298; R-24 to A-297; R-24 to I-296; R-24 to Q-295; R-24 to L-294; R-24 to Y-293; R-24 to T-292; R-24 to D-291; R-24 to Q-290; R-24 to R-289; R-24 to F-288; R-24 to A-287; R-24 to Q-286; R-24 to L-285; R-24 to R-284;

R-24 to Q-283; R-24 to R-282; R-24 to V-281; R-24 to E-280; R-24 to E-279; R-24 to S-278; R-24 to L-277; R-24 to M-276; R-24 to Q-275; R-24 to P-274; R-24 to D-273; R-24 to P-272; R-24 to G-271; R-24 to A-270; R-24 to G-269; R-24 to E-268; R-24 to E-267; R-24 to T-266; R-24 to G-265; R-24 to T-264; R-24 to G-263; R-24 to A-262;
5 R-24 to F-261; R-24 to A-260; R-24 to R-259; R-24 to I-258; R-24 to L-257; R-24 to E-256; R-24 to E-255; R-24 to R-254; R-24 to L-253; R-24 to Q-252; R-24 to D-251; R-24 to L-250; R-24 to N-249; R-24 to Q-248; R-24 to Q-247; R-24 to I-246; R-24 to R-245; R-24 to A-244; R-24 to H-243; R-24 to L-242; R-24 to A-241; R-24 to K-240; R-24 to A-239; R-24 to K-238; R-24 to L-237; R-24 to T-236; R-24 to L-235; R-24 to K-234; R-24 to R-233; R-24 to S-232; R-24 to L-231; R-24 to V-230; R-24 to Q-229; R-24 to V-228; R-24 to C-227; R-24 to R-226; R-24 to S-225; R-24 to L-224; R-24 to R-223; R-24 to A-222; R-24 to P-221; R-24 to S-220; R-24 to A-219; R-24 to P-218; R-24 to A-217; R-24 to H-216; R-24 to P-215; R-24 to A-214; R-24 to V-213; R-24 to S-212; R-24 to R-211; R-24 to H-210; R-24 to L-209; R-24 to E-208; R-24 to Q-207; R-24 to V-206; R-24 to H-205; R-24 to R-204; R-24 to G-203; R-24 to I-202; R-24 to G-201; R-24 to S-200; R-24 to V-199; R-24 to L-198; R-24 to S-197; R-24 to E-196; R-24 to A-195; R-24 to Y-194; R-24 to P-193; R-24 to H-192; R-24 to F-191; R-24 to L-190; R-24 to E-189; R-24 to K-188; R-24 to F-187; R-24 to R-186; R-24 to G-185; R-24 to T-184; R-24 to H-183; R-24 to H-182; R-24 to V-181; R-24 to V-180; R-24 to R-179; R-24 to S-178; R-24 to Q-177; R-24 to L-176; R-24 to G-175; R-24 to Q-174; R-24 to L-173; R-24 to L-172; R-24 to A-171; R-24 to W-170; R-24 to A-169; R-24 to E-168; R-24 to D-167; R-24 to V-166; R-24 to G-165; R-24 to G-164; R-24 to L-163; R-24 to L-162; R-24 to Q-161; R-24 to A-160; R-24 to K-159; R-24 to T-158; R-24 to D-157; R-24 to E-156; R-24 to G-155; R-24 to V-154; R-24 to V-153; R-24 to R-152; R-24 to L-151; R-24 to Q-150; R-24 to E-149; R-24 to Q-148; R-24 to L-147; R-24 to E-146; R-24 to Q-145; R-24 to V-144; R-24 to R-143; R-24 to L-142; R-24 to A-141; R-24 to V-140; R-24 to Q-139; R-24 to E-138; R-24 to M-137; R-24 to L-136; R-24 to D-135; R-24 to M-134; R-24 to T-133; R-24 to Y-132; R-24 to P-131; R-24 to K-130; R-24 to L-129; R-24 to Q-128; R-24 to Q-127; R-24 to R-126; R-24 to L-125; R-24 to G-124; R-24 to E-123; R-24 to L-122; R-24 to N-121; R-24 to W-120; R-24 to G-119; R-24 to V-118; R-24 to L-117; R-24 to E-116; R-24 to H-115; R-24 to A-114; R-24 to E-113; R-24 to A-112; R-24 to M-111; R-24 to Y-110; R-24 to P-109; R-

24 to Q-108; R-24 to L-107; R-24 to R-106; R-24 to A-105; R-24 to K-104; R-24 to V-103; R-24 to E-102; R-24 to E-101; R-24 to L-100; R-24 to E-99; R-24 to E-98; R-24 to Q-97; R-24 to L-96; R-24 to Q-95; R-24 to R-94; R-24 to R-93; R-24 to M-92; R-24 to G-91; R-24 to V-90; R-24 to P-89; R-24 to D-88; R-24 to Q-87; R-24 to P-86;
 5 R-24 to L-85; R-24 to R-84; R-24 to P-83; R-24 to A-82; R-24 to E-81; R-24 to S-80; R-24 to G-79; R-24 to S-78; R-24 to L-77; R-24 to P-76; R-24 to R-75; R-24 to L-74; R-24 to K-73; R-24 to E-72; R-24 to L-71; R-24 to F-70; R-24 to K-69; R-24 to N-68; R-24 to M-67; R-24 to N-66; R-24 to N-65; R-24 to L-64; R-24 to D-63; R-24 to Q-62; R-24 to E-61; R-24 to L-60; R-24 to S-59; R-24 to D-58; R-24 to K-57; R-24 to L-56; R-24 to T-55; R-24 to A-54; R-24 to P-53; R-24 to E-52; R-24 to R-51; R-24 to A-50; R-24 to M-49; R-24 to K-48; R-24 to Q-47; R-24 to Q-46; R-24 to H-45; R-24 to I-44; R-24 to Q-43; R-24 to E-42; R-24 to V-41; R-24 to R-40; R-24 to G-39; R-24 to K-38; R-24 to D-37; R-24 to G-36; R-24 to S-35; R-24 to T-34; R-24 to Q-33; R-24 to S-32; R-24 to F-31; R-24 to Y-30; of SEQ ID NO: 212. Polypeptides encoded by
 15 these polynucleotides are also encompassed by the invention. Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these
 20 polypeptides, or the complement thereof are encompassed by the invention. Antibodies that bind polypeptides of the invention are also encompassed by the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, the invention provides nucleic acid molecules having nucleotide
 25 sequences related to extensive portions of SEQ ID NO:19 which have been determined from the following related cDNA genes: HLDOE40R (SEQ ID NO:209), HLDOU12R (SEQ ID NO:210), and HLDBC83RA (SEQ ID NO:211).

Based on the sequence similarity to apolipoprotein A-IV of *Sus scrofa*, the human apolipoprotein A-IV, and the mouse apolipoprotein A-IV, translation product
 30 of this gene is expected to share at least some biological activities with apolipoproteins, and specifically apolipoprotein A-IV proteins. Such activities are known in the art, some of which are described elsewhere herein.

Specifically, polynucleotides and polypeptides of the invention are useful for the treatment, detection, and/or prevention of lipid transport & lipoprotein metabolism disorders. Polynucleotides and polypeptides are proposed to be associated with triglyceride-rich lipoproteins & HDL and may play a role in reverse cholesterol transport (cholesterol transport from tissues back to the liver for elimination). Thus, polynucleotides and polypeptides of the invention are useful for treating, detecting, and/or preventing hypercholesterolemia and related disorders. Polynucleotides and polypeptides of the invention are useful for activating lecithin cholesterol acyltransferase and the promotion of cholesterol efflux from cholesterol-preloaded cells. Polymorphisms in apoA-IV are associated with variability in low density lipoprotein (LDL)-cholesterol response to dietary therapy. Moreover, the levels of such polymorphisms (of the 32 currently known to exist in plasma) also appear to correlate with increased incidence and risk for coronary heart diseases. Thus, polynucleotides and polypeptides of the invention are useful for the treatment, detection, and/or prevention of cardiovascular diseases and/or disorders, particularly in the protection against atherogenesis in mice. Polynucleotides and polypeptides of the invention are useful as a satiating factor for controlling appetite and long-term regulation of food intake and body weight (chronic ingestion of a high fat diet blunts apoA-IV response to lipid feeding and may explain why chronic ingestion of a high fat diet predisposes animals and human to obesity).

Polynucleotides and polypeptides of the invention is involved in bile metabolism and is useful in the treatment, detection, and/or prevention of metabolism diseases and/or disorders, particularly for lipid metabolism and lipid emulsification. As inferred above, expression levels and/or polymorphisms in apoA-IV-L may represent diagnostic markers for such conditions as variability in low density lipoprotein (LDL)-cholesterol response to dietary therapy or bile disorders.

Polynucleotides and polypeptides of the invention may represent a diagnostic marker for atherogenesis, atherosclerosis, aberrant cholesterol/LDL/HDL plasma level regulation, obesity, hepatoma, liver diseases and/or disorders, metabolic diseases and/or disorders, obesity, and cardiovascular disease, in general. The full-length protein should be a secreted protein, based upon homology to the apolipoprotein family. Therefore, it is secreted into serum, urine, or feces and thus the levels is

assayable from patient samples. Assuming specific expression levels are reflective of the presence of metabolic dysfunction (e.g., aberrant cholesterol/LDL/HDL levels, bile synthesis dysfunction, lipoprotein metabolism dysfunction, etc.), this would provide a convenient diagnostic for early detection. In addition, expression of this gene product may also be linked to the progression of metabolic disease, and therefore
5 may itself actually represent a therapeutic or therapeutic target for the treatment of cancer.

Therefore, based upon the tissue distribution of this protein in liver, hepatoma, and pancreatic cells and tissues, in combination with its homology to apolipoproteins,
10 indicates that this protein represents a novel, central player in lipid transport and metabolism. Therefore, antagonists directed against this protein is useful in blocking the activity of this protein. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene.

Also provided is a kit for detecting tumors in which expression of this protein
15 occurs. Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, lymph, urine, seminal fluid, or feces and ascertaining
20 whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein.

Polynucleotides and polypeptides of the invention may play an important role
25 in the pathogenesis of human cancers and cellular transformation, particularly those of the gastrointestinal, endocrine, and metabolic systems, and specifically of hepatoma and pancreatic cancers. Polynucleotides and polypeptides of the invention may also be involved in the pathogenesis of developmental abnormalities based upon its potential effects on proliferation and differentiation of cells and tissue cell types. Due to the
30 potential proliferating and differentiating activity of said polynucleotides and polypeptides, the invention is useful as a therapeutic agent in inducing tissue regeneration, for treating inflammatory conditions (e.g., inflammatory bowel

syndrome, diverticulitis, etc.). Moreover, the invention is useful in modulating the immune response to aberrant polypeptides, as may exist in rapidly proliferating cells and tissue cell types, particularly in hepatoma cells, tissues, and other cancers.

The tissue distribution in hepatoma. Liver, and pancreatic cancer indicates
5 polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of metabolic and liver disorders. Representative uses are described in the "Hyperproliferative Disorders", "infectious disease", and "Binding Activity" sections below, in Example 11, and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of
10 hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells.

Alternatively, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental
15 diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation.

Dysregulation of apoptosis can result in inappropriate suppression of cell
20 death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA).

Alternatively, this gene product is involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of this
25 gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. In addition, other lipocalin family members, specifically cpl1, have been associated with playing a key role in early embryonic development. Through homology, it is expected that polypeptides and polynucleotides of the present invention may also play similar roles.
30 Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore,

the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions.

Thus this protein may modulate apoptosis or tissue differentiation and is useful
5 in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological
10 activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Preferred polypeptides of the present invention comprise, or alternatively
15 consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 111 as residues: Gln-19 to Trp-25, Tyr-27 to Arg-37, His-42 to Glu-49, Asp-55 to Asn-65, Glu-78 to Gln-84, Arg-91 to Glu-98, Glu-120 to Tyr-129, Gln-244 to Arg-251, Glu-265 to Gln-272, Ile-300 to Pro-313, Glu-324 to Gly-331.

Polynucleotides encoding said polypeptides are also encompassed by the invention.

20 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence
25 would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1379 of SEQ ID NO:40, b is an integer of 15 to 1393, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a
30 + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 31

The gene encoding the disclosed cDNA is believed to reside on chromosome 14. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 14.

It has been discovered that this gene is expressed in normal colon, colon
5 cancer, and ulcerative colitis. This gene is also expressed in normal breast tissue, breast lymph node, breast cancer, bone marrow, thymus, and tonsils.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions: gastrointestinal, hematopoietic,
10 immunological, and proliferative diseases and/or disorders, particularly colon cancer, and other cancers. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the gastrointestinal, hematopoietic, and immune systems, expression of
15 this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., bone marrow, gastrointestinal, digestive, immune, breast, cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, chyme, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from
20 an individual not having the disorder.

Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 112 as residues: Asp-73 to Asn-79, Ser-90 to Lys-97, Leu-105 to Ala-111, Tyr-127 to Gln-133, Ser-143 to Lys-148, Ser-156 to Gly-161, Arg-192 to Gly-202,
25 Leu-204 to Ser-209, Lys-229 to Asp-237, Pro-248 to Cys-264, Val-312 to Asp-319, Pro-336 to Thr-342, Lys-362 to Pro-369, Gly-408 to Tyr-417, Ser-422 to Thr-430, Asp-445 to Thr-451. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution in ulcerative colitis and colon cancer tissues indicates
30 that polynucleotides and polypeptides of the invention, as well as antibodies directed to polypeptides of the invention, are useful in the treatment, detection, and/or prevention of gastrointestinal disorders, including inflammatory bowel disorders and

proliferative diseases, particularly colon cancer. Furthermore, the expression of this gene in bone marrow, thymus, lymph node, and tonsil tissues suggests that polynucleotides and polypeptides of the invention, as well as antibodies directed to polypeptides of the invention, are useful in the detection, treatment, and/or prevention of hematopoietic and immunological disorders. Moreover, the expression within cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions, including colon and breast cancers. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Alternatively, this gene product may be involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention are useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein is useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Based upon the tissue distribution of this protein, antagonists directed against this protein may be useful in blocking the activity of this protein. Accordingly, preferred are

antibodies which specifically bind a portion of the translation product of this gene.

Also provided is a kit for detecting tumors in which expression of this protein occurs.

Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting

5 these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits
10 and methods), are more particularly described elsewhere herein. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or
15 immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
20 excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1637 of SEQ ID NO:41, b is an integer of 15 to 1651, where both a and b correspond to the positions of
25 nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 32

The translation product of this gene shares sequence homology with
30 complement subcomponent C1q chain C precursor (see Genbank accession S14351), which is thought to be important in immune responses.

It has been discovered that this gene is expressed primarily in immune and haemopoietic cells and to a lesser extent in various cancer cells.

Therefore, nucleic acids of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for
5 diagnosis of the following diseases and conditions: disorders of the immune and haemopoietic systems and cancer. Similarly, polypeptides and antibodies directed to those polypeptides are useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and haemopoietic systems, expression of
10 this gene at significantly higher or lower levels may be detected in certain tissues (e.g., cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

15 Preferred polypeptides of the present invention comprise, or alternatively consist of, one or more immunogenic epitopes immunogenic epitopes shown in SEQ ID NO: 113 as residues: Arg-25 to Gly-31, Pro-45 to Gly-52. Polynucleotides encoding said polypeptides are also encompassed by the invention.

The tissue distribution and homology to complement subcomponent C1q chain
20 C precursor suggests that the protein product of this clone would be useful for treatment and diagnosis of diseases of the immune and haemopoietic systems and cancers. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the
25 proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product is involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product is involved in immune
30 functions. Therefore it is also useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis,

acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus

5 erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the

10 differentiation and/or proliferation of various cell types. Based upon the tissue distribution of this protein, antagonists directed against this protein may be useful in blocking the activity of this protein. Accordingly, preferred are antibodies which specifically bind a portion of the translation product of this gene. Also provided is a kit for detecting tumors in which expression of this protein occurs. Such a kit

15 comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting these tumors in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid.

20 Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their

25 interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of

30 the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention

are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1094 of SEQ ID NO:42, b is an integer of 15 to 1108, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

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Table 1

Gene No.	cDNA Clone ID	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HSSDM23	PTA-736 09/21/99	Uni-ZAP XR	11	2329	1	2329	147	147	82	1	27	28	613
1	HSSDM23	PTA-736 09/21/99	Uni-ZAP XR	43	2286	1	2286	147	147	114	1	30	31	287
2	HOFNX30	PTA-736 09/21/99	pCMVSPORT 2.0	12	2330	1	2330	247	247	83	1	18	19	453
3	HLQFB12	PTA-736 09/21/99	Lambda ZAP II	13	651	1	651	52	52	84	1	20	21	152
4	HDPUM13	PTA-736 09/21/99	pCMVSPORT 3.0	14	997	1	997	16	16	85	1	22	23	245
4	HPLAT62	PTA-736 09/21/99	Uni-ZAP XR	44	1138	119	1075	128	128	115	1	24	25	245
4	HE6DI14	PTA-736 09/21/99	Uni-ZAP XR	45	1071	27	1071	50	50	116	1	24	25	245
4	HACBG19	PTA-2071 06/09/99	Uni-ZAP XR	46	1050	101	1002	107	107	117	1	22	23	229
4	HACBG19	PTA-2071 06/09/99	Uni-ZAP XR	47	1149	155	1149	128	128	118	1	22	23	245
4	HAPQT56	PTA-909 11/02/99	Uni-ZAP XR	48	1086	45	1012	64	64	119	1	22	23	245

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Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
4	HLYAN43	209226 08/28/97	pSport1	49	971	26	946	135	135	120	1	23	24	32
5	HTLGV19	PTA-736 09/21/99	Uni-ZAP XR	15	1266	1	1266	79	79	86	1	17	18	396
6	HTTCT46	PTA-736 09/21/99	Uni-ZAP XR	16	2710	93	2694	133	133	87	1	24	25	298
6	HSDEE58	PTA-909 11/02/99	Uni-ZAP XR	50	2752	97	1707	175	175	121	1	24	25	298
7	HOFNF53	PTA-736 09/21/99	pCMVSPORT 2.0	17	2405	1	2405	76	76	88	1	27	28	263
7	HOFNF53	PTA-736 09/21/99	pCMVSPORT 2.0	51	2389	1	2389	72	72	122	1	27	28	55
8	HOHCA60	PTA-627 09/07/99	pCMVSPORT 2.0	18	5720	1	5720	67	67	89	1	28	29	1745
8	HOHCA60	PTA-627 09/07/99	pCMVSPORT 2.0	52	2254	1177	2254		1021	123	1			19
8	HOHCA60	PTA-627 09/07/99	pCMVSPORT 2.0	53	3559	1	3559		1873	124	1	27	28	514
8	HOHCA60	PTA-627 09/07/99	pCMVSPORT 2.0	54	852	1	852	65	65	125	1	28	29	262
8	HOHCA60	PTA-627 09/07/99	pCMVSPORT 2.0	55	609	45	609		109	126	1	1	2	115

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Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
9	HLQFT18	PTA-736 09/21/99	Lambda ZAP II	19	705	1	705	16	16	90	1	20	21	142
10	HBXFT65	PTA-736 09/21/99	ZAP Express	20	2108	1	2085	130	130	91	1	16	17	350
10	HMSEO15	PTA-736 09/21/99	Uni-ZAP XR	56	2099	111	2027	114	114	127	1	17	18	350
11	HWHGK36	PTA-736 09/21/99	pCMVSPORT 3.0	21	675	1	675	12	12	92	1	24	25	102
12	HAGDA35	PTA-736 09/21/99	Uni-ZAP XR	22	1581	945	1581	53	53	93	1	37	38	509
12	HAGDA35	PTA-736 09/21/99	Uni-ZAP XR	57	1688	316	1688	366	366	128	1	28	29	339
12	HAGDA35	PTA-736 09/21/99	Uni-ZAP XR	58	1354	1	1354	39	39	129	1	28	29	339
13	HRODQ04	PTA-736 09/21/99	Uni-ZAP XR	23	922	1	922	193	193	94	1	26	27	146
14	HDPOL27	PTA-736 09/21/99	pCMVSPORT 3.0	24	2288	484	2271	115	115	95	1	30	31	626
14	HDPOL27	PTA-736 09/21/99	pCMVSPORT 3.0	59	1821	1	1821	137	137	130	1	29	30	472
14	HEBCV31	209194 08/01/97	Uni-ZAP XR	60	803	1	803	149	149	131	1			42

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Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
15	HWLHZ79	PTA-736 09/21/99	pSport1	25	908	1	871	85	85	96	1	24	25	81
16	HKGDP17	PTA-736 09/21/99	pSport1	26	2090	1	2090	348	348	97	1	14	15	86
17	HSVBD67	PTA-736 09/21/99	Uni-ZAP XR	27	2355	1588	2341	183	183	98	1	27	28	613
17	HSVBD67	PTA-736 09/21/99	Uni-ZAP XR	61	1499	1	1499	100	100	132	1	37	38	122
18	HTGAT51	PTA-736 09/21/99	Uni-ZAP XR	28	1680	1	1680	149	149	99	1	17	18	60
19	HFCEQ37	PTA-736 09/21/99	Uni-ZAP XR	29	1618	1	1577	78	78	100	1	18	19	167
20	HSKNP59	PTA-736 09/21/99	pBluescript	30	973	1	973	218	218	101	1	21	22	183
20	HSKNP59	PTA-736 09/21/99	pBluescript	62	974	1	974	218	218	133	1	21	22	252
21	HWMBB68	PTA-736 09/21/99	pSport1	31	1189	318	1189	50	50	102	1	30	31	239
21	HWMBB68	PTA-736 09/21/99	pSport1	63	872	1	871	64	64	134	1	18	19	132
21	HDTGF15	203570 01/11/99	pCMVSPORT 2.0	64	1208	27	1165	275	275	135	1	40	41	156

Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
21	HLWAD77	209651 03/04/98	pCMVSPORT 3.0	65	1167	304	1167	326	326	136	1	24	25	140
22	HWABL61	PTA-736 09/21/99	pCMVSPORT 3.0	32	1912	1	1912	218	218	103	1	39	40	89
23	HWDAQ83	PTA-736 09/21/99	pCMVSPORT 3.0	33	2394	1	2394	308	308	104	1	28	29	50
23	HWDAQ83	PTA-736 09/21/99	pCMVSPORT 3.0	66	2311	1	2311	308	308	137	1	31	32	50
24	HFRLF67	PTA-736 09/21/99	Lambda ZAP II	34	2118	1	2118	34	34	105	1	19	20	49
25	HTPHH74	PTA-736 09/21/99	Uni-ZAP XR	35	6065	2257	3272	162	162	106	1	30	31	868
25	HTPHH74	PTA-736 09/21/99	Uni-ZAP XR	67	1049	1	1016		1	138	1	1	2	172
25	HTFOB75	PTA-1838 05/09/00	pSport1	68	3299	1996	3274	2365	2365	139	1	46	47	142
26	HWABW88	PTA-736 09/21/99	pCMVSPORT 3.0	36	1365	1	1365	142	142	107	1	28	29	56
27	HWNFG66	PTA-797 09/27/99	pSport1	37	570	1	570	42	42	108	1	1	2	110
28	HDPQG01	PTA-736 09/21/99	pCMVSPORT 3.0	38	3229	1	3229	84	84	109	1	31	32	334

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Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
28	HDPQG01	PTA-736 09/21/99	pCMVSPORT 3.0	69	1772	1	1772	94	94	140	1	31	32	193
28	HJPAD80	PTA-840 10/13/99	Uni-ZAP XR	70	1121	1	1121	247	247	141	1	1	2	134
28	HTXJM94	PTA-181 06/07/99	Uni-ZAP XR	71	938	1	938	44	44	142	1	46	47	73
29	HE2IO57	PTA-736 09/21/99	Uni-ZAP XR	39	511	1	511	146	146	110	1	25	26	75
30	HLDRR08	PTA-796 09/27/99	pCMVSPORT 3.0	40	1393	1	1393	73	73	111	1	20	21	363
31	HTOJV86	PTA-736 09/21/99	Uni-ZAP XR	41	1651	1	1651	60	60	112	1	19	20	530
31	HHBGE77	PTA-736 09/21/99	pCMVSPORT 1	72	943	1	943	34	34	143	1	1	2	144
31	HCEFZ82	PTA-792 09/27/99	Uni-ZAP XR	73	1810	45	1780	215	215	144	1	18	19	189
31	HSIED48	PTA-987 11/24/99	Uni-ZAP XR	74	1543	1	1543	18	18	145	1	19	20	487
31	HADFW77	203980 04/29/99	pSport1	75	1806	935	1806	437	437	146	1	1	2	294
31	HNGFW58	203517 12/10/98	Uni-ZAP XR	76	1547	1	1547	279	279	147	1	28	29	99

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Gene No.	cDNA Clone ID	ATCC Deposit No.:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
31	HCEFZ82	203917 04/08/99	Uni-ZAP XR	77	1811	44	1781	215	215	148	1	18	19	265
32	HLYAV34	PTA-736 09/21/99	pSport1	42	1108	20	1108	117	117	113	1	32	33	207
32	HLYAV34	PTA-736 09/21/99	pSport1	78	1141	24	1141	105	105	149	1	32	33	206
32	HTOCG60	209368 10/16/97	Uni-ZAP XR	79	990	1	936	8	8	150	1	20	21	234
32	HDPWX42	203364 10/19/98	pCMVSPORT 3.0	80	1297	104	1237	184	184	151	1	28	29	208
32	HCNSM85	209300 09/25/97	pBluescript	81	941	1	941	16	16	152	1	22	23	235

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing) are sufficiently

accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also
5 hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used, for example, to generate antibodies which bind specifically to proteins containing the polypeptides and the secreted proteins encoded by the cDNA clones identified in Table 1.

10 Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the
15 actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the
20 generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods.
25 The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

30 The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed

herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or
5 species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or a deposited clone, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may
10 be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

Table 2 summarizes the expression profile of polynucleotides corresponding to the
15 clones disclosed in Table 1. The first column provides a unique clone identifier, "Clone ID", for a cDNA clone related to each contig sequence disclosed in Table 1. Column 2, "Library Codes" shows the expression profile of tissue and/or cell line libraries which express the polynucleotides of the invention. Each Library Code in column 2 represents a tissue/cell source identifier code corresponding to the Library
20 Code and Library description provided in Table 4. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. One of skill in the art could routinely use this information to identify tissues which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue
25 expression.

Table 3, column 1, provides a nucleotide sequence identifier, "SEQ ID NO:X," that matches a nucleotide SEQ ID NO:X disclosed in Table 1, column 5. Table 3, column 2, provides the chromosomal location, "Cytologic Band or Chromosome," of polynucleotides corresponding to SEQ ID NO:X. Chromosomal
30 location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Given a presumptive chromosomal location, disease locus association was

determined by comparison with the Morbid Map, derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM™. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>). If the putative chromosomal location of the Query overlapped with the chromosomal location of a Morbid Map entry, the OMIM reference identification number of the morbid map entry is provided in Table 3, column 3, labelled "OMIM ID." A key to the OMIM reference identification numbers is provided in Table 5.

10 Table 4 provides a key to the Library Code disclosed in Table 2. Column 1 provides the Library Code disclosed in Table 2, column 2. Column 2 provides a description of the tissue or cell source from which the corresponding library was derived.

15 Table 5 provides a key to the OMIM reference identification numbers disclosed in Table 3, column 3. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda, MD) 2000. World Wide Web
20 URL: <http://www.ncbi.nlm.nih.gov/omim/>). Column 2 provides diseases associated with the cytologic band disclosed in Table 3, column 2, as determined using the Morbid Map database.

Table 2

Clone ID	Library Codes
HSSDM23	H0008 H0012 H0040 H0052 H0059 H0087 H0135 H0140 H0166 H0252 H0253 H0254 H0265 H0309 H0327 H0333 H0370 H0483 H0484 H0486 H0494 H0506 H0509 H0520 H0521 H0539 H0542 H0545 H0547 H0556 H0586 H0617 H0619 H0620 H0646 H0658 H0672 H0673 H0684 H0689 L1290 S0007 S0011 S0031 S0038 S0040 S0053 S0144 S0222 S0282 S0356 S0358 S0376 S0388 S6016
HOFNX30	H0415
HLQFB12	H0059 H0150 H0204 H0331 H0393 H0509 H0510 H0574 H0615 H0661 L1290 S0358 S0360 S0374 S0410 S0444
HDPUM13	H0009 H0015 H0030 H0031 H0039 H0042 H0045 H0087 H0100 H0120 H0124 H0252 H0254 H0255 H0309 H0318 H0327 H0352 H0375 H0411 H0421 H0424 H0427 H0445 H0455 H0506 H0509 H0510 H0521 H0522 H0538 H0550 H0555 H0575 H0581 H0583 H0587 H0602 H0617 H0632 H0637 H0638 H0641 H0647 H0649 H0653 H0661 H0663 H0672 H0687 H0689 L1290 S0044 S0116 S0260 S0280 S0292 S0332 S0356 S0358 S0360 S0374 S0376 S0380 S0404 S0408 S0622 T0082
HTLGV19	H0284 H0555 H0618 H0620 L1290
HTTCT46	H0013 H0024 H0039 H0040 H0048 H0099 H0123 H0144 H0170 H0171 H0244 H0328 H0329 H0339 H0369 H0402 H0486 H0521 H0595 H0622 H0624 H0669 H0687 H0691 L1290 S0028 S0031 S0037 S0053 S0192 S0194 S0312 S0318 S0358 S0374 S0378 T0003 T0069
HOFNF53	H0415
HOHCA60	H0012 H0013 H0014 H0024 H0031 H0036 H0038 H0039 H0052 H0083 H0123 H0135 H0208 H0253 H0264 H0270 H0292 H0327 H0370 H0423 H0494 H0506 H0545 H0547 H0561 H0581 H0591 H0593 H0596 H0607 H0616 H0618 H0634 H0644 H0650 H0659 H0687 H0690 L0022 L1290 S0002 S0027 S0028 S0037 S0040 S0049 S0126 S0152 S0192 S0194 S0212 S0242 S0250 S0342 S0344 S0356 S0366 S0374 S0420 T0010 T0067 T0115
HLQFT18	H0059 H0150 H0204 H0331 H0393 H0509 H0510 H0574 H0615 H0661 L0022 S0358 S0360 S0374 S0410 S0444
HBXFT65	H0013 H0031 H0038 H0040 H0046 H0090 H0096 H0144 H0156 H0163 H0171 H0179 H0264 H0265 H0266 H0305 H0327 H0341 H0359 H0393 H0409 H0412 H0413 H0415 H0421 H0438 H0494 H0506 H0509 H0521 H0522 H0547 H0551 H0553 H0555 H0560 H0575 H0580 H0581 H0586 H0591 H0615 H0619 H0622 H0624 H0638 H0648 H0658 H0659 H0661 H0667 H0672 H0674 H0684 H0696 H0707 L0022 S0001 S0002 S0003 S0010 S0011 S0022 S0028 S0031 S0037 S0040 S0045 S0046 S0051 S0114 S0126 S0132 S0134 S0142 S0152 S0192 S0196 S0212 S0214 S0222 S0278 S0330 S0360 S0374 S0376 S0380 S0404 S0418 S0456 S0665 S6028 T0010 T0067 T0110
HWHGK36	H0024 H0032 H0087 H0150 H0188 H0379 H0392 H0494 H0555 H0586 H0587 H0592 H0600 H0604 H0620 H0670 H0689 L0022 S0126 S0192 S0352 S6024 T0067
HAGDA35	H0156 H0251 H0521 H0551 H0556 H0580 L0022 S0010 S0026 S0212 S0282
HRODQ04	H0494 H0497 H0519 H0551 H0580 H0586 H0598 H0599 H0624 L0022 S0040 S0150 S0180 S0212 S0312 S0314 S0380 S0386 T0040 T0082
HDPOL27	H0069 H0306 H0423 H0436 H0445 H0521 H0522 H0542 H0580 H0581

	H0591 H0596 H0624 H0638 H0648 L0022 S0002 S0007 S0222 S0426
HWLHZ79	H0232 H0512 H0597 L0022 S0044 S0330 S0354 S0358 S0374
HKGDP17	H0208 H0333 H0538 L0022
HSVBD67	H0008 H0012 H0013 H0014 H0040 H0052 H0059 H0087 H0135 H0140 H0166 H0179 H0252 H0253 H0254 H0265 H0266 H0268 H0309 H0327 H0333 H0370 H0392 H0483 H0484 H0486 H0494 H0506 H0509 H0519 H0520 H0521 H0539 H0542 H0545 H0547 H0551 H0556 H0580 H0581 H0586 H0593 H0617 H0619 H0620 H0643 H0646 H0657 H0658 H0659 H0660 H0672 H0673 H0674 H0684 H0689 H0690 L0022 S0007 S0011 S0031 S0038 S0040 S0053 S0140 S0144 S0192 S0222 S0282 S0356 S0358 S0376 S0388 S0424 S6016 S6022 S6024
HTGAT51	H0619 L0022 S0134
HFCEQ37	H0009 H0253 H0486 L0022 S0028 S0222 S0346
HSKNP59	L0022 S3012
HWMBB68	H0038 H0046 H0052 H0083 H0100 H0150 H0250 H0251 H0261 H0266 H0341 H0372 H0412 H0435 H0485 H0486 H0494 H0522 H0529 H0539 H0553 H0574 H0580 H0581 H0599 H0616 H0641 H0642 H0648 H0659 H0660 H0673 H0687 H0689 L0022 S0007 S0027 S0028 S0045 S0112 S0116 S0126 S0142 S0150 S0152 S0196 S0214 S0276 S0328 S0330 S0360 S0376 S0428 T0002 T0040 T0110
HWABL61	H0008 H0009 H0150 H0244 H0250 H0255 H0263 H0264 H0265 H0266 H0295 H0318 H0349 H0413 H0435 H0445 H0449 H0486 H0520 H0521 H0542 H0553 H0556 H0580 H0581 H0597 H0624 H0650 H0657 H0670 H0677 H0682 H0687 L0022 S0044 S0051 S0114 S0116 S0142 S0144 S0222 S0250 S0278 S0282 S0344 S0468 S6022 S6028 T0006
HWDAQ83	H0522 H0547 H0561 H0600 L0022
HFXLF67	S0282
HTPHH74	H0008 H0013 H0029 H0032 H0036 H0038 H0039 H0046 H0050 H0056 H0068 H0123 H0124 H0144 H0156 H0169 H0220 H0264 H0266 H0268 H0316 H0328 H0341 H0349 H0355 H0374 H0393 H0413 H0423 H0431 H0437 H0445 H0485 H0486 H0494 H0497 H0509 H0518 H0519 H0520 H0521 H0522 H0529 H0539 H0543 H0547 H0551 H0553 H0555 H0556 H0561 H0574 H0581 H0586 H0591 H0592 H0593 H0615 H0619 H0622 H0623 H0638 H0641 H0644 H0646 H0650 H0653 H0656 H0657 H0658 H0659 H0665 H0670 H0672 H0688 H0689 H0694 L0022 S0010 S0011 S0016 S0026 S0027 S0044 S0045 S0114 S0116 S0126 S0132 S0142 S0150 S0152 S0194 S0222 S0242 S0250 S0276 S0280 S0330 S0344 S0350 S0354 S0356 S0358 S0360 S0374 S0378 S0390 S0414 S0424 S0426 T0006 T0042 T0048 T0049
HWABW88	H0030 H0041 H0052 H0136 H0163 H0170 H0266 H0341 H0427 H0478 H0494 H0510 H0521 H0529 H0556 H0561 H0581 H0597 H0606 H0617 L0022 S0001 S0036 S0046 S0152 S0222 S0358 S0468 T0042 T0049
hwnfg66	S0360
HDPQG01	H0013 H0032 H0040 H0052 H0083 H0187 H0274 H0365 H0445 H0486 H0509 H0522 H0539 H0542 H0556 H0580 H0581 H0586 H0590 H0624 H0635 H0644 H0687 L0022 S0003 S0031 S0116 S0152 S0196 S0214 S0280 S0330 S0360 S0420 S0422 S0426 S6022 T0006
HE2IO57	H0031 H0050 H0170 H0263 H0318 H0327 H0341 H0411 H0412 H0413 H0422 H0506 H0521 H0545 H0547 H0556 H0575 H0580 H0581 H0586 H0599 H0623 H0638 H0646 H0659 H0672 H0687 L0022 S0003 S0040 S0114 S0208 S0212 S0214 S0242 S0418 S0420 S0422 S0458 S3014 T0004 T0071
hldrr08	H0509 H0510 S0380
HTOJV86	H0014 H0015 H0030 H0036 H0038 H0039 H0040 H0042 H0056 H0063

	H0085 H0087 H0090 H0135 H0144 H0163 H0179 H0183 H0188 H0194 H0204 H0205 H0231 H0232 H0234 H0235 H0251 H0252 H0254 H0255 H0263 H0264 H0271 H0272 H0274 H0318 H0328 H0355 H0373 H0375 H0383 H0402 H0421 H0427 H0436 H0444 H0478 H0479 H0485 H0486 H0488 H0489 H0506 H0510 H0518 H0519 H0521 H0522 H0538 H0551 H0553 H0560 H0575 H0581 H0586 H0587 H0590 H0596 H0597 H0614 L0022 S0003 S0026 S0031 S0044 S0052 S0116 S0122 S0216 S0282 S0312 S0314 S0328 S0330 S0354 S0356 S0358 S0360 S0372 S0374 S0376 S0382 S0394 S0404 S0406 S0430 S0432 S0440 S0442 S0444 S0446 S0448 S0456 S0464 T0002 T0023 T0082
HLYAV34	H0009 H0014 H0031 H0039 H0062 H0063 H0090 H0108 H0122 H0123 H0163 H0189 H0213 H0252 H0264 H0309 H0333 H0343 H0345 H0352 H0375 H0376 H0393 H0427 H0444 H0445 H0486 H0506 H0509 H0510 H0521 H0522 H0553 H0555 H0575 H0597 H0619 H0620 H0638 H0644 H0652 H0658 H0661 H0662 H0663 H0668 H0672 L0022 S0106 S0190 S0212 S0354 S0358 S0360 S0362 S0376 S0378 S0384

Table 3

SEQ ID NO: X	Cytologic Band or Chromosome:	OMIM Reference(s):
40	14q32.33	144120 147020 147110

Table 4

Library Code	Library Description
H0008	Whole 6 Week Old Embryo
H0009	Human Fetal Brain
H0012	Human Fetal Kidney
H0013	Human 8 Week Whole Embryo
H0014	Human Gall Bladder
H0015	Human Gall Bladder, fraction II
H0024	Human Fetal Lung III
H0029	Human Pancreas
H0030	Human Placenta
H0031	Human Placenta
H0032	Human Prostate
H0036	Human Adult Small Intestine
H0038	Human Testes
H0039	Human Pancreas Tumor
H0040	Human Testes Tumor
H0041	Human Fetal Bone
H0042	Human Adult Pulmonary
H0045	Human Esophagus, Cancer
H0046	Human Endometrial Tumor
H0048	Human Pineal Gland
H0050	Human Fetal Heart
H0052	Human Cerebellum
H0056	Human Umbilical Vein, Endo. remake
H0059	Human Uterine Cancer
H0062	Human Thymus
H0063	Human Thymus
H0068	Human Skin Tumor
H0069	Human Activated T-Cells
H0083	HUMAN JURKAT MEMBRANE BOUND POLYSOMES
H0085	Human Colon
H0087	Human Thymus
H0090	Human T-Cell Lymphoma
H0096	Human Parotid Cancer
H0099	Human Lung Cancer, subtracted
H0100	Human Whole Six Week Old Embryo
H0108	Human Adult Lymph Node, subtracted
H0120	Human Adult Spleen, subtracted
H0122	Human Adult Skeletal Muscle
H0123	Human Fetal Dura Mater
H0124	Human Rhabdomyosarcoma
H0135	Human Synovial Sarcoma
H0136	Supt Cells, cyclohexamide treated
H0140	Activated T-Cells, 8 hrs.
H0144	Nine Week Old Early Stage Human
H0150	Human Epididymus
H0156	Human Adrenal Gland Tumor
H0163	Human Synovium

H0166	Human Prostate Cancer, Stage B2 fraction
H0169	Human Prostate Cancer, Stage C fraction
H0170	12 Week Old Early Stage Human
H0171	12 Week Old Early Stage Human, II
H0179	Human Neutrophil
H0183	Human Colon Cancer
H0187	Resting T-Cell
H0188	Human Normal Breast
H0189	Human Resting Macrophage
H0194	Human Cerebellum, subtracted
H0204	Human Colon Cancer, subtracted
H0205	Human Colon Cancer, differential
H0208	Early Stage Human Lung, subtracted
H0213	Human Pituitary, subtracted
H0220	Activated T-Cells, 4 hrs, subtracted
H0231	Human Colon, subtraction
H0232	Human Colon, differential expression
H0234	human colon cancer, metastatic to liver, differentially expressed
H0235	Human colon cancer, metatized to liver, subtraction
H0244	Human 8 Week Whole Embryo, subtracted
H0250	Human Activated Monocytes
H0251	Human Chondrosarcoma
H0252	Human Osteosarcoma
H0253	Human adult testis, large inserts
H0254	Breast Lymph node cDNA library
H0255	breast lymph node CDNA library
H0261	H. cerebellum, Enzyme subtracted
H0263	human colon cancer
H0264	human tonsils
H0265	Activated T-Cell (12hs)/Thiouridine labelledEco
H0266	Human Microvascular Endothelial Cells, fract. A
H0268	Human Umbilical Vein Endothelial Cells, fract. A
H0270	HPAS (human pancreas, subtracted)
H0271	Human Neutrophil, Activated
H0272	HUMAN TONSILS, FRACTION 2
H0274	Human Adult Spleen, fractionII
H0284	Human OB MG63 control fraction I
H0292	Human OB HOS treated (10 nM E2) fraction I
H0295	Amniotic Cells - Primary Culture
H0305	CD34 positive cells (Cord Blood)
H0306	CD34 depleted Buffy Coat (Cord Blood)
H0309	Human Chronic Synovitis
H0316	HUMAN STOMACH
H0318	HUMAN B CELL LYMPHOMA
H0327	human corpus colosum
H0328	human ovarian cancer
H0329	Dermatofibrosarcoma Protuberance
H0331	Hepatocellular Tumor
H0333	Hemangiopericytoma
H0339	Duodenum
H0341	Bone Marrow Cell Line (RS4,11)
H0343	stomach cancer (human)
H0345	SKIN

H0349	human adult liver cDNA library
H0352	wilm's tumor
H0355	Human Liver
H0359	KMH2 cell line
H0365	Osteoclastoma-normalized B
H0369	H. Atrophic Endometrium
H0370	H. Lymph node breast Cancer
H0372	Human Testes
H0373	Human Heart
H0374	Human Brain
H0375	Human Lung
H0376	Human Spleen
H0379	Human Tongue, frac 1
H0383	Human Prostate BPH, re-excision
H0392	H. Meningima, M1
H0393	Fetal Liver, subtraction II
H0402	CD34 depleted Buffy Coat (Cord Blood), re-excision
H0409	H. Striatum Depression, subtracted
H0411	H Female Bladder, Adult
H0412	Human umbilical vein endothelial cells, IL-4 induced
H0413	Human Umbilical Vein Endothelial Cells, uninduced
H0415	H. Ovarian Tumor, II, OV5232
H0421	Human Bone Marrow, re-excision
H0422	T-Cell PHA 16 hrs
H0423	T-Cell PHA 24 hrs
H0424	Human Pituitary, subt IX
H0427	Human Adipose
H0431	H. Kidney Medulla, re-excision
H0435	Ovarian Tumor 10-3-95
H0436	Resting T-Cell Library,II
H0437	H Umbilical Vein Endothelial Cells, frac A, re-excision
H0438	H. Whole Brain #2, re-excision
H0444	Spleen metastatic melanoma
H0445	Spleen, Chronic lymphocytic leukemia
H0449	CD34+ cell, I
H0455	H. Striatum Depression, subt
H0478	Salivary Gland, Lib 2
H0479	Salivary Gland, Lib 3
H0483	Breast Cancer cell line, MDA 36
H0484	Breast Cancer Cell line, angiogenic
H0485	Hodgkin's Lymphoma I
H0486	Hodgkin's Lymphoma II
H0488	Human Tonsils, Lib 2
H0489	Crohn's Disease
H0494	Keratinocyte
H0497	HEL cell line
H0506	Ulcerative Colitis
H0509	Liver, Hepatoma
H0510	Human Liver, normal
H0512	Keratinocyte, lib 3
H0518	pBMC stimulated w/ poly I/C
H0519	NTERA2, control
H0520	NTERA2 + retinoic acid, 14 days

H0521	Primary Dendritic Cells, lib 1
H0522	Primary Dendritic cells,frac 2
H0529	Myeloid Progenitor Cell Line
H0538	Merkel Cells
H0539	Pancreas Islet Cell Tumor
H0542	T Cell helper I
H0543	T cell helper II
H0545	Human endometrial stromal cells-treated with progesterone
H0547	NTERA2 teratocarcinoma cell line+retinoic acid (14 days)
H0550	H. Epididymus, cauda
H0551	Human Thymus Stromal Cells
H0553	Human Placenta
H0555	Rejected Kidney, lib 4
H0556	Activated T-cell(12h)/Thiouridine-re-excision
H0560	KMH2
H0561	L428
H0574	Hepatocellular Tumor, re-excision
H0575	Human Adult Pulmonary, re-excision
H0580	Dendritic cells, pooled
H0581	Human Bone Marrow, treated
H0583	B Cell lymphoma
H0586	Healing groin wound, 6.5 hours post incision
H0587	Healing groin wound, 7.5 hours post incision
H0590	Human adult small intestine, re-excision
H0591	Human T-cell lymphoma, re-excision
H0592	Healing groin wound - zero hr post-incision (control)
H0593	Olfactory epithelium, nasal cavity
H0595	Stomach cancer (human), re-excision
H0596	Human Colon Cancer, re-excision
H0597	Human Colon, re-excision
H0598	Human Stomach, re-excision
H0599	Human Adult Heart, re-excision
H0600	Healing Abdomen wound, 70&90 min post incision
H0602	Healing Abdomen Wound, 21&29 days post incision
H0604	Human Pituitary, re-excision
H0606	Human Primary Breast Cancer, re-excision
H0607	H. Leukocytes, normalized cot 50A3
H0614	H. Leukocytes, normalized cot 500 A
H0615	Human Ovarian Cancer Reexcision
H0616	Human Testes, Reexcision
H0617	Human Primary Breast Cancer Reexcision
H0618	Human Adult Testes, Large Inserts, Reexcision
H0619	Fetal Heart
H0620	Human Fetal Kidney, Reexcision
H0622	Human Pancreas Tumor, Reexcision
H0623	Human Umbilical Vein, Reexcision
H0624	12 Week Early Stage Human II, Reexcision
H0632	Hepatocellular Tumor, re-excision
H0634	Human Testes Tumor, re-excision
H0635	Human Activated T-Cells, re-excision
H0637	Dendritic Cells From CD34 Cells
H0638	CD40 activated monocyte dendritic cells
H0641	LPS activated derived dendritic cells

H0642	Hep G2 Cells, lambda library
H0643	Hep G2 Cells, PCR library
H0644	Human Placenta (re-excision)
H0646	Lung, Cancer (4005313 A3): Invasive Poorly Differentiated Lung Adenocarcinoma,
H0647	Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic
H0648	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low Malignant Pot
H0649	Lung, Normal: (4005313 B1)
H0650	B-Cells
H0652	Lung, Normal: (4005313 B1)
H0653	Stromal Cells
H0656	B-cells (unstimulated)
H0657	B-cells (stimulated)
H0658	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma
H0659	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma
H0660	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma
H0661	Breast, Cancer: (4004943 A5)
H0662	Breast, Normal: (4005522B2)
H0663	Breast, Cancer: (4005522 A2)
H0665	Stromal cells 3.88
H0667	Stromal cells(HBM3.18)
H0668	stromal cell clone 2.5
H0669	Breast, Cancer: (4005385 A2)
H0670	Ovary, Cancer(4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma
H0672	Ovary, Cancer: (4004576 A8)
H0673	Human Prostate Cancer, Stage B2, re-excision
H0674	Human Prostate Cancer, Stage C, re-excision
H0677	TNFR degenerate oligo
H0682	Ovarian cancer, Serous Papillary Adenocarcinoma
H0684	Ovarian cancer, Serous Papillary Adenocarcinoma
H0687	Human normal ovary(#9610G215)
H0688	Human Ovarian Cancer(#9807G017)
H0689	Ovarian Cancer
H0690	Ovarian Cancer, # 9702G001
H0691	Normal Ovary, #9710G208
H0694	Prostate cancer (adenocarcinoma)
H0696	Prostate Adenocarcinoma
H0707	Stomach Cancer(S007635)
L0022	Soares pregnant uterus NbHPU
L1290	Soares NFL T GBC S1
S0001	Brain frontal cortex
S0002	Monocyte activated
S0003	Human Osteoclastoma
S0007	Early Stage Human Brain
S0010	Human Amygdala
S0011	STROMAL -OSTEOCLASTOMA
S0016	Kidney Pyramids
S0022	Human Osteoclastoma Stromal Cells - unamplified
S0026	Stromal cell TF274
S0027	Smooth muscle, serum treated
S0028	Smooth muscle,control

S0031	Spinal cord
S0036	Human Substantia Nigra
S0037	Smooth muscle, IL1b induced
S0038	Human Whole Brain #2 - Oligo dT > 1.5Kb
S0040	Adipocytes
S0044	Prostate BPH
S0045	Endothelial cells-control
S0046	Endothelial-induced
S0049	Human Brain, Striatum
S0051	Human Hypothalamus,Schizophrenia
S0052	neutrophils control
S0053	Neutrophils IL-1 and LPS induced
S0106	STRIATUM DEPRESSION
S0112	Hypothalamus
S0114	Anergic T-cell
S0116	Bone marrow
S0122	Osteoclastoma-normalized A
S0126	Osteoblasts
S0132	Epithelial-TNFa and INF induced
S0134	Apoptotic T-cell
S0140	eosinophil-IL5 induced
S0142	Macrophage-oxLDL
S0144	Macrophage (GM-CSF treated)
S0150	LNCAP prostate cell line
S0152	PC3 Prostate cell line
S0180	Bone Marrow Stroma, TNF&LPS ind
S0190	Prostate BPH,Lib 2, subtracted
S0192	Synovial Fibroblasts (control)
S0194	Synovial hypoxia
S0196	Synovial IL-1/TNF stimulated
S0208	Messangial cell, frac 1
S0212	Bone Marrow Stromal Cell, untreated
S0214	Human Osteoclastoma, re-excision
S0216	Neutrophils IL-1 and LPS induced
S0222	H. Frontal cortex,epileptic,re-excision
S0242	Synovial Fibroblasts (III/TNF), sub
S0250	Human Osteoblasts II
S0260	Spinal Cord, re-excision
S0276	Synovial hypoxia-RSF subtracted
S0278	H Macrophage (GM-CSF treated), re-excision
S0280	Human Adipose Tissue, re-excision
S0282	Brain Frontal Cortex, re-excision
S0292	Osteoarthritis (OA-4)
S0312	Human osteoarthritic,fraction II
S0314	Human osteoarthritis,fraction I
S0318	Human Normal Cartilage Fraction II
S0328	Palate carcinoma
S0330	Palate normal
S0332	Pharynx carcinoma
S0342	Adipocytes,re-excision
S0344	Macrophage-oxLDL, re-excision
S0346	Human Amygdala,re-excision
S0350	Pharynx Carcinoma

S0352	Larynx Carcinoma
S0354	Colon Normal II
S0356	Colon Carcinoma
S0358	Colon Normal III
S0360	Colon Tumor II
S0362	Human Gastrocnemius
S0366	Human Soleus
S0372	Larynx carcinoma III
S0374	Normal colon
S0376	Colon Tumor
S0378	Pancreas normal PCA4 No
S0380	Pancreas Tumor PCA4 Tu
S0382	Larynx carcinoma IV
S0384	Tongue carcinoma
S0386	Human Whole Brain, re-excision
S0388	Human Hypothalamus, schizophrenia, re-excision
S0390	Smooth muscle, control, re-excision
S0394	Stomach, normal
S0404	Rectum normal
S0406	Rectum tumour
S0408	Colon, normal
S0410	Colon, tumour
S0414	Hippocampus, Alzheimer Subtracted
S0418	CHME Cell Line, treated 5 hrs
S0420	CHME Cell Line, untreated
S0422	Mo7e Cell Line GM-CSF treated (1ng/ml)
S0424	TF-1 Cell Line GM-CSF Treated
S0426	Monocyte activated, re-excision
S0428	Neutrophils control, re-excision
S0430	Aryepiglottis Normal
S0432	Sinus piriformis Tumour
S0440	Liver Tumour Met 5 Tu
S0442	Colon Normal
S0444	Colon Tumor
S0446	Tongue Tumour
S0448	Larynx Normal
S0456	Tongue Normal
S0458	Thyroid Normal (SDCA2 No)
S0464	Larynx Normal
S0468	Ea.hy.926 cell line
S0665	Human Amygdala, re-excision
S3012	Smooth Muscle Serum Treated, Norm
S3014	Smooth muscle, serum induced, re-exc
S6016	H. Frontal Cortex, Epileptic
S6022	H. Adipose Tissue
S6024	Alzheimers, spongy change
S6028	Human Manic Depression Tissue
T0002	Activated T-cells
T0003	Human Fetal Lung
T0004	Human White Fat
T0006	Human Pineal Gland
T0010	Human Infant Brain
T0023	Human Pancreatic Carcinoma

T0040	HSC172 cells
T0042	Jurkat T-Cell, S phase
T0048	Human Aortic Endothelium
T0049	Aorta endothelial cells + TNF-a
T0067	Human Thyroid
T0069	Human Uterus, normal
T0071	Human Bone Marrow
T0082	Human Adult Retina
T0110	Human colon carcinoma (HCC) cell line, remake
T0115	Human Colon Carcinoma (HCC) cell line

Table 5

OMIM ID	OMIM Description
144120	Hyperimmunoglobulin G1 syndrome (2) (?)
147020	Agammaglobulinemia, 601495 (3)
147110	IgG2 deficiency, selective (3)

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification , such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the secreted protein.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or a cDNA contained in ATCC deposit Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y and/or a polypeptide encoded by the cDNA contained in ATCC deposit Z. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y and/or a polypeptide sequence encoded by the cDNA contained in ATCC deposit Z are also encompassed by the invention.

Signal Sequences

The present invention also encompasses mature forms of the polypeptide having the polypeptide sequence of SEQ ID NO:Y and/or the polypeptide sequence encoded by the cDNA in a deposited clone. Polynucleotides encoding the mature forms (such as, for example, the polynucleotide sequence in SEQ ID NO:X and/or the

polynucleotide sequence contained in the cDNA of a deposited clone) are also encompassed by the invention. According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretary leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough
5 endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species of the protein. Further, it has long been known that cleavage specificity of a secreted protein is ultimately determined by the primary structure of
10 the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide.

Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, *Virus Res.* 3:271-286 (1985), uses the information from a short N-terminal
15 charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, *Nucleic Acids Res.* 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of
20 these methods is in the range of 75-80%. (von Heinje, *supra*.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et
25 al., *Protein Engineering* 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.

30 As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence

shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the
5 polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal
10 sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. Nonetheless, the present invention provides the mature protein produced by expression of the polynucleotide sequence of SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited
15 clone, in a mammalian cell (e.g., COS cells, as described below). These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Polynucleotide and Polypeptide Variants

The present invention is directed to variants of the polynucleotide sequence
20 disclosed in SEQ ID NO:X, the complementary strand thereto, and/or the cDNA sequence contained in a deposited clone.

The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y and/or encoded by a deposited clone.

"Variant" refers to a polynucleotide or polypeptide differing from the
25 polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%,
30 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for example, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence contained in a deposited cDNA clone or the

complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in a deposited clone, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein).

- 5 Polynucleotides which hybridize to these nucleic acid molecules under stringent hybridization conditions or lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

The present invention is also directed to polypeptides which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%,
10 95%, 96%, 97%, 98%, 99% identical to, for example, the polypeptide sequence shown in SEQ ID NO:Y, the polypeptide sequence encoded by the cDNA contained in a deposited clone, and/or polypeptide fragments of any of these polypeptides (e.g., those fragments described herein).

By a nucleic acid having a nucleotide sequence at least, for example, 95%
15 "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95%
20 identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1, the ORF (open reading frame), or any fragment specified
25 as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best
30 overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp.

App. Biosci. 6:237-245(1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to
5 calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3'
10 deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are
15 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected
20 score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query
25 sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score
30 calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the

deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, an amino acid sequences shown in Table 1 (SEQ ID NO:Y) or to the amino acid sequence encoded by cDNA contained in a deposited clone can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245(1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window

Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not

matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing
5 alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced
10 for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an
15 organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA
20 technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after
25 deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., *J. Biotechnology* 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological
30 activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (*J. Biol. Chem* 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over

3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, 5 Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological 10 functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic 15 activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the 20 art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural 25 selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid 30 substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used.

- 5 (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification or (v) fusion of the polypeptide with another compound, such as albumin (including, but not limited to, recombinant albumin (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of the present invention having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a peptide or polypeptide to have an amino acid sequence which comprises the amino acid sequence of the present invention, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of the present invention or fragments thereof (e.g., the mature form and/or other fragments described herein), is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

Polynucleotide and Polypeptide Fragments

The present invention is also directed to polynucleotide fragments of the polynucleotides of the invention.

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence which: is a portion of that contained in a deposited clone, or encoding the polypeptide encoded by the cDNA in a deposited clone; is a portion of that shown in SEQ ID NO:X or the complementary strand thereto, or is a portion of a polynucleotide sequence encoding the polypeptide of SEQ ID NO:Y. The nucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt,

and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in a deposited clone or the nucleotide sequence shown in SEQ ID NO:X. In this context "about" includes the particularly recited value, a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to these nucleic acid molecules under stringent hybridization conditions or lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y or encoded by the cDNA contained in a deposited clone. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40,

41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, and ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions. Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotides encoding these domains are also contemplated.

Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

Preferably, the polynucleotide fragments of the invention encode a polypeptide which demonstrates a functional activity. By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) polypeptide of invention protein. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide of the invention for binding) to an antibody to the polypeptide of the invention], immunogenicity (ability to generate antibody which binds to a polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

The functional activity of polypeptides of the invention, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the invention for binding to an antibody of the polypeptide of the invention, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

In another embodiment, where a ligand for a polypeptide of the invention identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel

chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky, E., et al., 1995, Microbiol. Rev. 59:94-123. In another embodiment, physiological correlates of binding of a polypeptide of the invention to its substrates (signal transduction) can be assayed.

5 In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the invention and fragments, variants derivatives and analogs thereof to elicit related biological activity related to that of the polypeptide of the invention (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope
10 of the invention.

Epitopes and Antibodies

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID
15 NO:Y, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. Z or encoded by a polynucleotide that hybridizes to the complement of the sequence of SEQ ID NO:X or contained in ATCC deposit No. Z under stringent hybridization conditions or lower stringency hybridization conditions as defined supra. The present invention further encompasses
20 polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or lower
25 stringency hybridization conditions defined supra.

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide
30 encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies

described *infra*. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross-reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211).

In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985)). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to

an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very
5 least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., *J. Gen. Virol.*, 66:2347-
10 2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS),
15 while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an
20 immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the
25 peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention comprising an immunogenic or antigenic epitope can be fused to other polypeptide sequences. For example, the polypeptides
30 of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof), or albumin (including but not limited to recombinant

albumin (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life in vivo. This has been shown

5 for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an

10 FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*,

15 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991,

20 *Proc. Natl. Acad. Sci. USA* 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni²⁺

25 nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to

30 modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721;

5,834,252; and 5,837,458, and Patten et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Antibodies

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin

molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')₂, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, by size in contiguous amino acid residues, or listed in the Tables and Figures. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be

excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog,

5 ortholog, or homolog of a polypeptide of the present invention are included.

Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present

10 invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using

15 methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the

20 present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention

may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation
25 constant or K_d less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M.

The invention also provides antibodies that competitively inhibit binding of an
30 antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the

epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes
5 antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand
10 binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described
15 supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent
20 ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but
25 do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists
30 for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No.

5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

10 Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g.,
15 Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

 As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus
20 or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438;
25 WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

 The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include
30 antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of

numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

5 The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of- interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal
10 antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and
15 potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

 Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be
20 produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not
25 limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

 Methods for producing and screening for specific antibodies using hybridoma
30 technology are routine and well known in the art and are discussed in detail in the Examples (e.g., Example 16). In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an

immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are
5 selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating
10 monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody
15 able to bind a polypeptide of the invention.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')₂ fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments).
20 F(ab')₂ fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which
25 carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid
30 surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage

gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., *J. Immunol. Methods* 182:41-50 (1995); Ames et al., *J. Immunol. Methods* 184:177-186 (1995); Kettleborough et al., *Eur. J. Immunol.* 24:952-958 (1994); Persic
5 et al., *Gene* 187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225;
10 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and
15 expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')₂ fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); and Sawai et al., *AJRI* 34:26-
20 34 (1995); and Better et al., *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology* 203:46-88 (1991); Shu et al., *PNAS* 90:7995-7999
25 (1993); and Skerra et al., *Science* 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal
30 antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Gillies et al., (1989) *J. Immunol.*

Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entirety.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into

mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention.

10 Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA,

15 IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European

20 Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar

25 to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et

30 al., *Bio/technology* 12:899-903 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using

techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be
5 used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to
10 bind its ligands/receptors, and thereby block its biological activity.

Polynucleotides Encoding Antibodies

The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The
15 invention also encompasses polynucleotides that hybridize under stringent or lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

20 The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the
25 synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a
30 particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library

generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe
5 specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the
10 antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor,
15 NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entirety), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light
20 chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted
25 within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of
30 the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino

acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423-42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038-1041 (1988)).

Methods of Producing Antibodies

The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a

polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as

bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems
5 infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO,
10 BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole
15 recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2
20 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which
25 direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic
30 Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such

fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the
5 GST moiety.

In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus
10 and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric
15 gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad.
20 Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and
25 initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression
30 of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein.

Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgp^rt- or ap^rt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt,

which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 5 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215); and hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. 10 (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

15 The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in 20 culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second 25 vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic 30 free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for
5 the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

10 The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through
15 linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention
20 to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS
25 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may
30 be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any

combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., *Proc. Natl. Acad. Sci. USA* 88:10535-10539 (1991); Zheng et al., *J. Immunol.* 154:5590-5600 (1995); and Vil et al., *Proc. Natl. Acad. Sci. USA* 89:11337-11341(1992) (said references incorporated by reference in their entireties).

As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., *Nature* 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., *J. Biochem.* 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to

identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred
5 embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags
10 useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used
15 diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent
20 materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No.
25 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone,
30 fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin,

and aequorin; and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{111}In or ^{99}Tc .

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi . A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, α -interferon, β -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- α , TNF- β , AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGF (See, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"),

granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports
5 include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld
10 et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results,
15 And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

20 Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can
25 be used as a therapeutic.

Immunophenotyping

The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present
30 invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific

epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with
5 antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to
10 prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

15 The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions,
20 gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by
25 reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1%
30 Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A

and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., ³²P or ¹²⁵I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes

the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

10 The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., ^3H or ^{125}I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., ^3H or ^{125}I) in the presence of increasing amounts of an unlabeled second antibody.

Therapeutic Uses

25 The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any

one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or
5 conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the
10 antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

15 The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

20 The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment,
25 human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and
30 therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention,

including fragments thereof. Preferred binding affinities include those with a dissociation constant or K_d less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, and 10^{-15} M.

Gene Therapy

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990).

In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other

desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific

5 embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or
10 indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be
15 accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun;
20 Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target
25 cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT
30 Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination

(Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435-438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages,

neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

5 In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or
10 progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

15 In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

20 *Demonstration of Therapeutic or Prophylactic Activity*

The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition
25 include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a
30 specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment;

this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when
5 administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)
10

In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another
15 embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., *Macromol. Sci. Rev.* *Macromol. Chem.* 23:61 (1983); see also Levy et al., *Science* 228:190 (1985); During et al., *Ann. Neurol.* 25:351 (1989); Howard et al., *J. Neurosurg.* 71:105 (1989)). In yet
20 another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, supra, vol. 2, pp. 115-138 (1984)).
25

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote
30 expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by

use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g.,
5 Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a
10 pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic
15 is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid
20 carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering
25 agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium
30 saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of

the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human
5 antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the
10 antibodies by modifications such as, for example, lipidation.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture,
15 use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Diagnosis and Imaging

Labeled antibodies, and derivatives and analogs thereof, which specifically
20 bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body
25 fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

The invention provides a diagnostic assay for diagnosing a disorder,
30 comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level,

whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{125}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{112}In), and technetium (^{99}Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods

including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce
5 diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of
10 Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the
15 labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by
20 repeating the method for diagnosing the disease or disorder, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label
25 used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

30 In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with

a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is
5 detected in a patient using magnetic resonance imaging (MRI).

Kits

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified
10 antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present
15 invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

20 In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically
25 immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide
30 antigen. The polypeptide antigen of the kit may also be attached to a solid support.

In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may

also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

5 In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be
10 a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present
15 invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the
20 reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip
25 sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated
30 antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound

recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Fusion Proteins

5 Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target
10 cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

 Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur
15 through linker sequences.

 Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell
20 or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

 Moreover, polypeptides of the present invention, including fragments, and
25 specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins
30 consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988).)

Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995).) Polynucleotides comprising or alternatively consisting of
5 nucleic acids which encode these fusion proteins are also encompassed by the invention.

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a
10 fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for
15 example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker
20 sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for
25 instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides
30 or the polypeptides of the present invention.

Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli* lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera Sf9* cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A,

pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-

mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some
5 proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In one embodiment, the yeast *Pichia pastoris* is used to express the polypeptide of the present invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A
10 main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O₂. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O₂. Consequently, in a growth medium depending on methanol as a main
15 carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See, Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., *et al.*, *Yeast* 5:167-77 (1989); Tschopp, J.F., *et al.*, *Nucl. Acids Res.* 15:3859-76 (1987).

20 Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

In one example, the plasmid vector pPIC9K is used to express DNA encoding
25 a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a protein of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal
30 peptide (i.e., leader) located upstream of a multiple cloning site.

Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with the polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination, resulting in the formation of a new transcription unit (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; U.S. Patent No. 5,733,761, issued March 31, 1998; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., Nature, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a

polypeptide sequence of the invention can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the
5 common amino acids, 2,4-diaminobutyric acid, α -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ -Abu, ϵ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β -alanine, fluoro-
10 amino acids, designer amino acids such as β -methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

The invention encompasses polypeptides which are differentially modified during or after translation, *e.g.*, by glycosylation, acetylation, phosphorylation,
15 amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH_4 ; acetylation, formylation, oxidation, reduction; metabolic
20 synthesis in the presence of tunicamycin; etc.

Additional post-translational modifications encompassed by the invention include, for example, *e.g.*, N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and
25 addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Also provided by the invention are chemically modified derivatives of the
30 polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent NO: 4,179,337). The chemical moieties for

derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al.*, *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev *et al.*, *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti *et al.*, *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik *et al.*, *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may

be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992); Francis *et al.*, *Intern. J. of Hematol.* 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($\text{ClSO}_2\text{CH}_2\text{CF}_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

The number of polyethylene glycol moieties attached to each protein of the invention (*i.e.*, the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12,

15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992).

The polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, *Therapeutics*) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or encoded by the cDNA contained in a deposited clone (including fragments, variants, splice variants, and fusion proteins, corresponding to these polypeptides as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (*e.g.*, containing polypeptides having identical or different amino acid sequences) or a homotrimer (*e.g.*, containing polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (*i.e.*, polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional

embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in the sequence listing, or contained in the polypeptide encoded by a deposited clone). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein of the invention.

In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in an Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, ositeoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627

(hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Another method for preparing multimer polypeptides of the invention involves
5 use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different
10 proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide
15 sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are
20 those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

25 In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-
30 Flag® antibody.

The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers

of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

5 Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, 10 e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein 20 technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic 25 polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides 30 of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into

liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Uses of the Polynucleotides

5 Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

 The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers,
10 since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

 Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be
15 selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

20 Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled
25 flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety)..

 Precise chromosomal location of the polynucleotides can also be achieved
30 using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see

Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g., Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder.

In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the present invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the present invention, where each probe has one strand containing a 31'-mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

Where a diagnosis of a disorder, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the present invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

By "measuring the expression level of polynucleotide of the present invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the present invention or the level of the mRNA encoding the polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or

estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having a disorder. As will be appreciated in the art, once a standard polypeptide
5 level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains the polypeptide of the present invention or mRNA. As indicated, biological samples
10 include body fluids (such as semen, lymph, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and other tissue sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred
15 source.

The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174.
20 Further, such a gene chip with polynucleotides of the present invention attached may be used to identify polymorphisms between the polynucleotide sequences, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, including cancerous diseases and conditions. Such a
25 method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the
30 preferred form if the polynucleotides are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine,

thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, *Science* 254, 1497 (1991); and M. Egholm, O. Buchardt, L.Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, *Nature* 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point ($T_{sub.m}$) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

The present invention is useful for detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

Pathological cell proliferative diseases, disorders, and/or conditions are often associated with inappropriate activation of proto-oncogenes. (Germann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in *Neoplastic Diseases of the Blood*, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal

cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Gelmann et al., supra) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Gelmann et al., supra) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Gelmann et al., supra)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580) However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness would not be limited to treatment of proliferative diseases, disorders, and/or conditions of hematopoietic cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456

(1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while
5 antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat or prevent disease.

Polynucleotides of the present invention are also useful in gene therapy. One
10 goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

15 The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for
20 identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative
25 to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an
30 individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression

in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell. Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (^{125}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{112}In), and technetium ($^{99\text{m}}\text{Tc}$), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I , ^{112}In , $^{99\text{m}}\text{Tc}$), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of $^{99\text{m}}\text{Tc}$. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Moreover, polypeptides of the present invention can be used to treat, prevent, and/or diagnose disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat, prevent, and/or diagnose disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also

be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

5

Gene Therapy Methods

Another aspect of the present invention is to gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of a polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the invention that operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the invention *ex vivo*, with the engineered cells then being provided to a patient to be treated with the polypeptide. Such methods are well-known in the art. For example, see Beldegrun et al., J. Natl. Cancer Inst., 85:207-216 (1993); Ferrantini et al., Cancer Research, 53:107-1112 (1993); Ferrantini et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura et al., Cancer Research 50: 5102-5106 (1990); Santodonato, et al., Human Gene Therapy 7:1-10 (1996); Santodonato, et al., Gene Therapy 4:1246-1255 (1997); and Zhang, et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver,

and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

In one embodiment, the polynucleotide of the invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences
5 that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such
10 methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

The polynucleotide vector constructs of the invention used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors
15 include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

Any strong promoter known to those skilled in the art can be used for driving
20 the expression of polynucleotide sequence of the invention. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter;
25 the ApoA1 promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotides of the invention.

Unlike other gene therapy techniques, one major advantage of introducing
30 naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA

sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct of the invention can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked *nucleic acid* sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

5 The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

 In certain embodiments, the polynucleotide constructs of the invention are complexed in a liposome preparation. Liposomal preparations for use in the instant
10 invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA ,
15 84:7413-7416 (1987), which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA , 86:6077-6081 (1989), which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem., 265:10189-10192 (1990), which is herein incorporated by reference), in functional form.

20 Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA , 84:7413-7416 (1987), which is herein incorporated by reference). Other commercially
25 available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

 Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication NO: WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of
30 DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., Felgner et al., Proc.

Natl. Acad. Sci. USA, 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily
5 available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these
10 materials are well known in the art.

For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be
15 prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at
20 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar
25 vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology, 101:512-527 (1983), which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass
30 tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a

suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+} -EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta, 394:483 (1975); Wilson et al., Cell, 17:77 (1979)); ether injection (Deamer et al., Biochim. Biophys. Acta, 443:629 (1976); Ostro et al., Biochem. Biophys. Res. Commun., 76:836 (1977); Fraley et al., Proc. Natl. Acad. Sci. USA, 76:3348 (1979)); detergent dialysis (Enoch et al., Proc. Natl. Acad. Sci. USA, 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem., 255:10431 (1980); Szoka et al., Proc. Natl. Acad. Sci. USA, 75:145 (1978); Schaefer-Ridder et al., Science, 215:166 (1982)), which are herein incorporated by reference.

Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ratio will be from about 5:1 to about 1:5. More preferably, the ratio will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

U.S. Patent NO: 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication NO: WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication NO: WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding polypeptides of the invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis

virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected
5 include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy, 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation,
10 the use of liposomes, and CaPO_4 precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding polypeptides of the invention. Such retroviral vector
15 particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express polypeptides of the invention.

In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with polynucleotides of the invention contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses polypeptides of the invention, and
20 at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz et al., Am. Rev. Respir. Dis.,
25 109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld et al., Science, 252:431-434 (1991); Rosenfeld et al., Cell, 68:143-155 (1992)). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative
30 (Green et al. Proc. Natl. Acad. Sci. USA, 76:6606 (1979)).

Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel., 3:499-503 (1993);

Rosenfeld et al., Cell , 68:143-155 (1992); Engelhardt et al., Human Genet. Ther., 4:759-769 (1993); Yang et al., Nature Genet., 7:362-369 (1994); Wilson et al., Nature , 365:691-692 (1993); and U.S. Patent NO: 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: Ela, Elb, E3, E4, E2a, or L1 through L5.

In certain other embodiments, the cells are engineered, *ex vivo* or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, Curr. Topics in Microbiol. Immunol., 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct containing polynucleotides of the invention is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including

lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct of the invention.

- 5 These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express the desired gene product.

Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding the
10 polypeptide sequence of interest) via homologous recombination (see, e.g., U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA, 86:8932-8935 (1989); and Zijlstra et al., Nature, 342:435-438 (1989). This method
15 involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently
20 complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

25 The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the
30 amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can
5 be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such
10 that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

The polynucleotides encoding polypeptides of the present invention may be administered along with other polynucleotides encoding other angiogenic proteins. Angiogenic proteins include, but are not limited to, acidic and basic fibroblast growth
15 factors, VEGF-1, VEGF-2 (VEGF-C), VEGF-3 (VEGF-B), epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

20 Preferably, the polynucleotide encoding a polypeptide of the invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be
25 homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct
30 needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid

(tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the
5 rat livers. (Kaneda et al., Science, 243:375 (1989)).

A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting
10 the composition centimeters and preferably, millimeters within arteries.

Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue
15 inside the wound.

Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a
20 particular site.

Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad.
25 Sci. USA, 189:11277-11281 (1992), which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a
30 polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian. Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly

Biological Activities

The polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides or polypeptides, or agonists or antagonists could be used to treat the associated disease.

Immune Activity

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of

the present invention can be used as a marker or detector of a particular immune system disease or disorder.

Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein diseases, disorders, and/or conditions (e.g., agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing autoimmune disorders. Many autoimmune disorders result from inappropriate

recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides and polypeptides of the invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Autoimmune diseases or disorders that may be treated, prevented, and/or diagnosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following:

10 autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia,

15 Polyendocrinopathies, Purpura (e.g., Henloch-Schoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, Autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis, systemic lupus erythematosus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as,

20 as, for example, (a) Graves' Disease, (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia, idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA

25 nephropathy, bullous pemphigoid, Sjogren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiomy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous,

30 degenerative, and atrophic disorders.

Additional autoimmune disorders (that are probable) that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are

not limited to, rheumatoid arthritis (often characterized, e.g., by immune complexes in joints), scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g.,
5 ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by
10 glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic
15 drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

Additional autoimmune disorders (that are possible) that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle
20 antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondrial antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial
25 antibodies), cardiomyopathy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

30 In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated,

prevented, and/or diagnosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention.

In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost
5 immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

B cell immunodeficiencies that may be ameliorated or treated by administering the polypeptides or polynucleotides of the invention, and/or agonists thereof, include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-
10 linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia,
15 agammaglobulinemia, common variable immunodeficiency (CVI) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa
20 chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof
25 syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

T cell deficiencies that may be ameliorated or treated by administering the polypeptides or polynucleotides of the invention, and/or agonists thereof include, but
30 are not limited to, for example, DiGeorge anomaly, thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia,

immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity. In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are ameliorated or treated by, for example, administering the polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

Other immunodeficiencies that may be ameliorated or treated by administering polypeptides or polynucleotides of the invention, and/or agonists thereof, include, but are not limited to, severe combined immunodeficiency (SCID; e.g., X-linked SCID, autosomal SCID, and adenosine deaminase deficiency), ataxia-telangiectasia, Wiskott-Aldrich syndrome, short-limber dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome (e.g., purine nucleoside phosphorylase deficiency), MHC Class II deficiency. In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are ameliorated or treated by administering the polypeptides or polynucleotides of the invention, and/or agonists thereof.

In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, and/or diagnosed using antibodies against the protein of the invention.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, and/or diagnosed using polypeptides, antibodies, or polynucleotides of the invention, and/or

agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Moreover, inflammatory conditions may also be treated, diagnosed, and/or prevented with polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. Such inflammatory conditions include, but are not limited to, for example, respiratory disorders (such as, e.g., asthma and allergy); gastrointestinal disorders (such as, e.g., inflammatory bowel disease); cancers (such as, e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (such as, e.g., multiple sclerosis, blood-brain barrier permeability, ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (such as, e.g., Parkinson's disease and Alzheimer's disease), AIDS-related dementia, and prion disease); cardiovascular disorders (such as, e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (such as, e.g., chronic hepatitis (B and C), rheumatoid arthritis, gout, trauma, septic shock, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus (i.e., type 1 diabetes), and allogenic transplant rejection).

In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to treat, diagnose, and/or prevent transplantation rejections, graft-versus-host disease, autoimmune and inflammatory diseases (e.g., immune complex-induced vasculitis, glomerulonephritis, hemolytic anemia, myasthenia gravis, type II collagen-induced arthritis, experimental allergic and hyperacute xenograft rejection, rheumatoid arthritis, and systemic lupus erythematosus (SLE). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also be used to modulate and/or diagnose inflammation. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to treat, diagnose, or prognose, inflammatory conditions, both chronic and acute conditions, including, but not limited to, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, and resulting from over production of cytokines (e.g., TNF or IL-1.).

Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

Additional preferred embodiments of the invention include, but are not limited to, the use of polypeptides, antibodies, polynucleotides and/or agonists or antagonists in the following applications:

Administration to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

Administration to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741.

A vaccine adjuvant that enhances immune responsiveness to specific antigen.

An adjuvant to enhance tumor-specific immune responses.

10 An adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, 15 or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, Respiratory syncytial virus, Dengue, Rotavirus, Japanese B encephalitis, Influenza A and B, 20 Parainfluenza, Measles, Cytomegalovirus, Rabies, Junin, Chikungunya, Rift Valley fever, Herpes simplex, and yellow fever.

An adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria 25 or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B. In another specific embodiment, the compositions of the invention are used as 30 an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Meisseria meningitidis*,

Streptococcus pneumoniae, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, *Borrelia burgdorferi*, and Plasmodium (malaria).

5 An adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an
10 adjuvant to enhance an immune response to Plasmodium (malaria).

As a stimulator of B cell responsiveness to pathogens.

As an activator of T cells.

As an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

15 As an agent to induce higher affinity antibodies.

As an agent to increase serum immunoglobulin concentrations.

As an agent to accelerate recovery of immunocompromised individuals.

As an agent to boost immunoresponsiveness among aged populations.

As an immune system enhancer prior to, during, or after bone marrow
20 transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific
25 embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

As an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell
30 function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are

not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

As an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, recovery from surgery.

As a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonization of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

As an agent to direct an individuals immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

As a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

As a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodeficiency.

As a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect.

As a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence such as observed among SCID patients.

As an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

As a means of activating T cells.

As a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leshmania.

As pretreatment of bone marrow samples prior to transplant. Such treatment would increase B cell representation and thus accelerate recover.

5 As a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

Additionally, polypeptides or polynucleotides of the invention, and/or agonists thereof, may be used to treat or prevent IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema.

10 All of the above described applications as they may apply to veterinary medicine.

Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, or ribozymes. These would be expected to reverse many of the activities of the ligand described above as well as find clinical or
15 practical application as:

A means of blocking various aspects of immune responses to foreign agents or self. Examples include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and pathogens.

20 A therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythramatosus and MS.

An inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in
25 disrupting immune responses, and blocking sepsis.

An inhibitor of graft versus host disease or transplant rejection.

A therapy for B cell and/or T cell malignancies such as ALL, Hodgkins disease, non-Hodgkins lymphoma, Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, and EBV-transformed diseases.

30 A therapy for chronic hypergammaglobulinemeia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

A therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

A means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

An immunosuppressive agent(s).

5 Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

In another embodiment, administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention, may be used to treat or prevent IgE-mediated allergic reactions including, but not limited to, asthma,
10 rhinitis, and eczema.

The agonists and antagonists may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

The agonists or antagonists may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of
15 neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain auto-immune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes. The antagonists or agonists may also be employed to treat infectious diseases including
20 silicosis, sarcoidosis, idiopathic pulmonary fibrosis by, for example, preventing the recruitment and activation of mononuclear phagocytes. They may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration. The antagonists or agonists or may also be employed for treating atherosclerosis, for example, by preventing monocyte
25 infiltration in the artery wall.

Antibodies against polypeptides of the invention may be employed to treat ARDS.

Agonists and/or antagonists of the invention also have uses in stimulating wound and tissue repair, stimulating angiogenesis, stimulating the repair of vascular
30 or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to treat or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii.

In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to treat, diagnose, and/or prevent (1) cancers or neoplasms and (2) autoimmune cell or tissue-related cancers or neoplasms. In a preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat, diagnose, and/or prevent acute myelogenous leukemia. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat, diagnose, and/or prevent, chronic myelogenous leukemia, multiple myeloma, non-Hodgkins lymphoma, and/or Hodgkins disease.

In another specific embodiment, polynucleotides or polypeptides, and/or agonists or antagonists of the invention may be used to treat, diagnose, prognose, and/or prevent selective IgA deficiency, myeloperoxidase deficiency, C2 deficiency, ataxia-telangiectasia, DiGeorge anomaly, common variable immunodeficiency (CVI),

X-linked agammaglobulinemia, severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), and Wiskott-Aldrich syndrome.

Examples of autoimmune disorders that can be treated or detected are described above and also include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prognosed, prevented, and/or diagnosed using antibodies against the polypeptide of the invention.

As an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

Additionally, polynucleotides, polypeptides, and/or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related

glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangi endotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and

brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Hyperproliferative diseases and/or disorders that could be detected and/or treated by polynucleotides, polypeptides, and/or antagonists of the invention, include, but are not limited to neoplasms located in the: liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to:

hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Hyperproliferative Disorders

A polynucleotides or polypeptides, or agonists or antagonists of the invention can be used to treat, prevent, and/or diagnose hyperproliferative diseases, disorders, and/or conditions, including neoplasms. A polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative diseases, disorders, and/or conditions can be treated, prevented, and/or diagnosed. This immune response may
5 be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating, preventing, and/or diagnosing hyperproliferative diseases, disorders, and/or conditions, such as a chemotherapeutic agent.

Examples of hyperproliferative diseases, disorders, and/or conditions that can
10 be treated, prevented, and/or diagnosed by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral),
15 lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative diseases, disorders, and/or conditions can also be treated, prevented, and/or diagnosed by a polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative diseases, disorders, and/or conditions include, but are not limited to:
20 hypergammaglobulinemia, lymphoproliferative diseases, disorders, and/or conditions, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

One preferred embodiment utilizes polynucleotides of the present invention to
25 inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

Thus, the present invention provides a method for treating or preventing cell proliferative diseases, disorders, and/or conditions by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said
30 polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating or preventing cell-proliferative diseases, disorders, and/or conditions in individuals

comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said

5 polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform

10 non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said

15 polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

Polynucleotides of the present invention may be useful in repressing

20 expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the

25 normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any

30 other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature

320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference.

5 In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes
10 needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use
15 of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts,
20 which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the
25 polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in
30 tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating, preventing, and/or diagnosing one or more of the described diseases, disorders, and/or conditions. Methods for
5 producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may
10 be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of
15 the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

In particular, the antibodies, fragments and derivatives of the present invention are useful for treating, preventing, and/or diagnosing a subject having or developing cell proliferative and/or differentiation diseases, disorders, and/or conditions as
20 described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example, which serve to increase the number or
25 activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of diseases, disorders, and/or conditions related to polynucleotides or
30 polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those

with a dissociation constant or K_d less than $5 \times 10^{-6}M$, $10^{-6}M$, $5 \times 10^{-7}M$, $10^{-7}M$, $5 \times 10^{-8}M$, $10^{-8}M$, $5 \times 10^{-9}M$, $10^{-9}M$, $5 \times 10^{-10}M$, $10^{-10}M$, $5 \times 10^{-11}M$, $10^{-11}M$, $5 \times 10^{-12}M$, $10^{-12}M$, $5 \times 10^{-13}M$, $10^{-13}M$, $5 \times 10^{-14}M$, $10^{-14}M$, $5 \times 10^{-15}M$, and $10^{-15}M$.

Moreover, polypeptides of the present invention are useful in inhibiting the
5 angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in
combination with other polypeptides directly or indirectly, as described elsewhere
herein. In a most preferred embodiment, said anti-angiogenesis effect may be
achieved indirectly, for example, through the inhibition of hematopoietic, tumor-
specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl
10 Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference).
Antibodies directed to polypeptides or polynucleotides of the present invention may
also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al.,
Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by
reference)).

15 Polypeptides, including protein fusions, of the present invention, or fragments
thereof may be useful in inhibiting proliferative cells or tissues through the induction
of apoptosis. Said polypeptides may act either directly, or indirectly to induce
apoptosis of proliferative cells and tissues, for example in the activation of a death-
domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1),
20 TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related
apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al.,
Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference).
Moreover, in another preferred embodiment of the present invention, said
polypeptides may induce apoptosis through other mechanisms, such as in the
25 activation of other proteins which will activate apoptosis, or through stimulating the
expression of said proteins, either alone or in combination with small molecule drugs
or adjuvants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins
(See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33
(1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12
30 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by
reference).

Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as
5 activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering
10 compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodies of the invention may be associated with with heterologous polypeptides,
15 heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present
20 invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

Cardiovascular Disorders

25 Polynucleotides or polypeptides, or agonists or antagonists of the invention may be used to treat, prevent, and/or diagnose cardiovascular diseases, disorders, and/or conditions, including peripheral artery disease, such as limb ischemia.

Cardiovascular diseases, disorders, and/or conditions include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral
30 arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus

arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's
5 Syndrome, trilogy of Fallot, ventricular heart septal defects.

Cardiovascular diseases, disorders, and/or conditions also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea,
10 cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease,
15 rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial
20 block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic
25 junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

Heart valve disease include aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve
30 insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial
5 reperfusion injury, and myocarditis.

Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms,
10 angiodyplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular diseases, disorders, and/or conditions, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis,
15 erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer,
20 vasculitis, and venous insufficiency.

Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

Arterial occlusive diseases include arteriosclerosis, intermittent claudication,
25 carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

Cerebrovascular diseases, disorders, and/or conditions include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral
30 arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural

hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

Embolisms include air embolisms, amniotic fluid embolisms, cholesterol
5 embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

Ischemia includes cerebral ischemia, ischemic colitis, compartment
10 syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

15 Polynucleotides or polypeptides, or agonists or antagonists of the invention, are especially effective for the treatment of critical limb ischemia and coronary disease.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous
20 injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides of the invention may be administered as part of a *Therapeutic*,
25 described in more detail below. Methods of delivering polynucleotides of the invention are described in more detail herein.

Anti-Angiogenesis Activity

The naturally occurring balance between endogenous stimulators and
30 inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound

healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye diseases, disorders, and/or conditions, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

The present invention provides for treatment of diseases, disorders, and/or conditions associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, *Medicine*, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating, preventing, and/or diagnosing an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat or prevent a cancer or tumor. Cancers which may be treated, prevented, and/or diagnosed with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors,

including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat or prevent cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating, preventing, and/or diagnosing other diseases, disorders, and/or conditions, besides cancers, which involve angiogenesis. These diseases, disorders, and/or conditions include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

For example, within one aspect of the present invention methods are provided for treating, preventing, and/or diagnosing hypertrophic scars and keloids, comprising

the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating, preventing, and/or diagnosing neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

Moreover, Ocular diseases, disorders, and/or conditions associated with neovascularization which can be treated, prevented, and/or diagnosed with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity, macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthalmol.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalmol.* 22:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating or preventing neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of

diseases, disorders, and/or conditions can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause),
5 toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in
10 eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-
15 angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent
20 complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing
25 front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed
30 between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-

3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

Within another aspect of the present invention, methods are provided for treating or preventing neovascular glaucoma, comprising the step of administering to
5 a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat or prevent early forms of neovascular glaucoma. Within other
10 embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating or preventing proliferative diabetic retinopathy, comprising the step of
15 administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide,
20 polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

Within another aspect of the present invention, methods are provided for treating or preventing retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist
25 and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

Additionally, diseases, disorders, and/or conditions which can be treated, prevented, and/or diagnosed with the polynucleotides, polypeptides, agonists and/or
30 agonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome,

pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

Moreover, diseases, disorders, and/or conditions and/or states, which can be treated, prevented, and/or diagnosed with the the polynucleotides, polypeptides, agonists and/or agonists include; but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uvetitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochela minalia quintosa), ulcers (*Helicobacter pylori*), Bartonellosis and bacillary angiomatosis.

. In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized

to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat
5 tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti-angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized
10 during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide,
15 agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the
20 anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

Within one aspect of the present invention, polynucleotides, polypeptides,
25 agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

30 The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive

Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

5 Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

10 Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

15 Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo
20 molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example,
25 molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

 A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4;
30 protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence

of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; 5 Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; 10 alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

15

Diseases at the Cellular Level

Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, and/or diagnosed by the polynucleotides or polypeptides and/or antagonists or agonists of the invention, include cancers (such as 20 follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast 25 cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune diseases, disorders, and/or conditions (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and 30 adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, the polynucleotides or polypeptides, and/or

agonists or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated, prevented or diagnosed by the polynucleotides or polypeptides, or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated, prevented, and/or diagnosed by the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative diseases, disorders, and/or conditions (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune diseases, disorders, and/or conditions (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis,

Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g.,
5 hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

10 In accordance with yet a further aspect of the present invention, there is provided a process for utilizing the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds.
15 Polynucleotides or polypeptides, as well as agonists or antagonists of the invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat
20 exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to promote dermal reestablishment subsequent to dermal
25 loss

The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are a non-exhaustive list of grafts that polynucleotides or polypeptides, agonists or antagonists
30 of the invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft,

epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omentum graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, can be used to promote skin strength and to improve the appearance of aged skin.

It is believed that the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, may have a cytoprotective effect on the small intestine mucosa. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. The polynucleotides or polypeptides, and/or

agonists or antagonists of the invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to treat diseases associate with the under expression of the polynucleotides of the invention.

Moreover, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to prevent and heal damage to the lungs due to various pathological states. A growth factor such as the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated, prevented, and/or diagnosed using the polynucleotides or polypeptides, and/or agonists or antagonists of the invention. Also, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary dysplasia, in premature infants.

The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could stimulate the proliferation and differentiation of hepatocytes and,

thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetrachloride and other hepatotoxins known in the art).

5 In addition, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to maintain the islet function so as to alleviate, delay or
10 prevent permanent manifestation of the disease. Also, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

15 **Neurological Diseases**

Nervous system diseases, disorders, and/or conditions, which can be treated, prevented, and/or diagnosed with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases, disorders, and/or conditions which
20 result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated, prevented, and/or diagnosed in a patient (including human and non-human mammalian patients) according to the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1)
25 ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of
30 the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is

destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases, disorders, and/or conditions, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

In a preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat, prevent, and/or diagnose neural cell injury associated with cerebral hypoxia. In one aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose neural cell injury associated with cerebral ischemia. In another aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose neural cell injury associated with cerebral infarction. In another aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose or prevent neural cell injury associated with a stroke. In a further aspect of this embodiment, the polypeptides, polynucleotides, or agonists

or antagonists of the invention are used to treat, prevent, and/or diagnose neural cell injury associated with a heart attack.

The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, e.g., choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, the method set forth in Arakawa et al. (J. Neurosci. 10:3507-3515 (1990)); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk et al. (Exp. Neurol. 70:65-82 (1980)) or Brown et al. (Ann. Rev. Neurosci. 4:17-42 (1981)); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

In specific embodiments, motor neuron diseases, disorders, and/or conditions that may be treated, prevented, and/or diagnosed according to the invention include, but are not limited to, diseases, disorders, and/or conditions such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as diseases, disorders, and/or conditions that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-

Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary
Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

Further, polypeptides or polynucleotides of the invention may play a role in
neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus,
5 compositions of the invention (including polynucleotides, polypeptides, and agonists
or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders
associated with these roles, including, but not limited to, learning and/or cognition
disorders. The compositions of the invention may also be useful in the treatment or
prevention of neurodegenerative disease states and/or behavioural disorders. Such
10 neurodegenerative disease states and/or behavioral disorders include, but are not
limited to, Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette
Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder,
panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors,
including disorders in feeding, sleep patterns, balance, and perception. In addition,
15 compositions of the invention may also play a role in the treatment, prevention and/or
detection of developmental disorders associated with the developing embryo, or
sexually-linked disorders.

Additionally, polypeptides, polynucleotides and/or agonists or antagonists of
the invention, may be useful in protecting neural cells from diseases, damage,
20 disorders, or injury, associated with cerebrovascular disorders including, but not
limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or
Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral
anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery
diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus
25 thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or
subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral
ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or
vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia,
periventricular, and vascular headache (e.g., cluster headache or migraines).

30 In accordance with yet a further aspect of the present invention, there is
provided a process for utilizing polynucleotides or polypeptides, as well as agonists or
antagonists of the present invention, for therapeutic purposes, for example, to

stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or
5 detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency,
10 pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as
15 ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

20 Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral
25 arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency,
30 vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as
5 Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome,
10 Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic
15 epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure
20 hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural
25 empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention
30 include meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis which includes lymphocytic choriomeningitis, Bacterial meningitis which includes Haemophilus Meningitis, Listeria Meningitis, Meningococcal Meningitis such as

Waterhouse-Friderichsen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uve-meningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes
5 bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention
10 include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral
15 sceloris which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue
20 Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's
25 Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon-Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett
30 Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity,

encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention

5 include hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia,

10 apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia,

15 broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia,

20 myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic

25 Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism,

30 spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron

disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Infectious Disease

A polypeptide or polynucleotide and/or agonist or antagonist of the present invention can be used to treat, prevent, and/or diagnose infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated, prevented, and/or diagnosed. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polypeptide or polynucleotide and/or agonist or antagonist of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Bimaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat, prevent, and/or diagnose any of these symptoms or

diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention
5 are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose AIDS.

Similarly, bacterial or fungal agents that can cause disease or symptoms and
10 that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Cryptococcus neoformans, Aspergillosis, Bacillaceae
15 (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia (e.g., Borrelia burgdorferi), Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, E. coli (e.g., Enterotoxigenic E. coli and Enterohemorrhagic E. coli), Enterobacteriaceae (Klebsiella, Salmonella (e.g., Salmonella typhi, and Salmonella paratyphi), Serratia, Yersinia), Erysipelothrix,
20 Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Mycobacterium leprae, Vibrio cholerae, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Meisseria meningitidis, Pasteurellacea Infections (e.g., Actinobacillus, Heamophilus (e.g., Heamophilus influenza type B), Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, Shigella spp.,
25 Staphylococcal, Meningiococcal, Pneumococcal and Streptococcal (e.g., Streptococcus pneumoniae and Group B Streptococcus). These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia,
30 prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea,

meningitis (e.g., meningitis types A and B), Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections.

5 Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat, prevent, and/or diagnose: tetanus, Diphtheria, botulism, and/or meningitis type B.

10 Moreover, parasitic agents causing disease or symptoms that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, 15 Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., Plasmodium virax, Plasmodium falciparum, Plasmodium malariae and Plasmodium ovale). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS 20 related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose malaria.

25 Preferably, treatment or prevention using a polypeptide or polynucleotide and/or agonist or antagonist of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the 30 polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

A polynucleotide or polypeptide and/or agonist or antagonist of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues
5 could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs
10 (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide and/or agonist or antagonist of the
15 present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide and/or agonist or antagonist of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated, prevented, and/or diagnosed include of tendinitis, carpal tunnel
20 syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a
polynucleotide or polypeptide and/or agonist or antagonist of the present invention to
25 proliferate and differentiate nerve cells. Diseases that could be treated, prevented, and/or diagnosed using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic diseases, disorders, and/or conditions (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral
30 neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-

Drager syndrome), could all be treated, prevented, and/or diagnosed using the polynucleotide or polypeptide and/or agonist or antagonist of the present invention.

Chemotaxis

5 A polynucleotide or polypeptide and/or agonist or antagonist of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then
10 fight off and/or heal the particular trauma or abnormality.

 A polynucleotide or polypeptide and/or agonist or antagonist of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat, prevent, and/or diagnose inflammation, infection, hyperproliferative diseases, disorders, and/or conditions, or any immune system
15 disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat, prevent, and/or diagnose wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat, prevent, and/or diagnose wounds.

20 It is also contemplated that a polynucleotide or polypeptide and/or agonist or antagonist of the present invention may inhibit chemotactic activity. These molecules could also be used to treat, prevent, and/or diagnose diseases, disorders, and/or conditions. Thus, a polynucleotide or polypeptide and/or agonist or antagonist of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

 A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit
30 (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural
5 receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell
10 membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

15 The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations,
20 polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

25 Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which a polypeptide of the invention binds can be
30 identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein

polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labelled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of polypeptides of the invention thereby effectively generating agonists and antagonists of polypeptides of the invention. See generally, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, S. Trends Biotechnol. 16(2):76-82 (1998); Hansson, L. O., et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. Biotechniques 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides of the invention may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired polynucleotide

sequence of the invention molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides of the invention may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In
5 another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptides of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a
10 growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs),
15 nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptides of the invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide. The
20 biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the
25 polypeptide of the present invention, the compound to be screened and 3[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the
30 uptake of 3[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of

3[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat, prevent, and/or diagnose disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues. Therefore, the invention includes a method of identifying compounds which bind to the polypeptides of the invention comprising the steps of: (a) incubating a candidate binding compound with the polypeptide; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with the polypeptide, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Also, one could identify molecules bind a polypeptide of the invention experimentally by using the beta-pleated sheet regions contained in the polypeptide sequence of the protein. Accordingly, specific embodiments of the invention are directed to polynucleotides encoding polypeptides which comprise, or alternatively consist of, the amino acid sequence of each beta pleated sheet regions in a disclosed polypeptide sequence. Additional embodiments of the invention are directed to polynucleotides encoding polypeptides which comprise, or alternatively consist of,

any combination or all of contained in the polypeptide sequences of the invention. Additional preferred embodiments of the invention are directed to polypeptides which comprise, or alternatively consist of, the amino acid sequence of each of the beta pleated sheet regions in one of the polypeptide sequences of the invention. Additional
5 embodiments of the invention are directed to polypeptides which comprise, or alternatively consist of, any combination or all of the beta pleated sheet regions in one of the polypeptide sequences of the invention.

Targeted Delivery

10 In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or
15 prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic
20 protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific
25 destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of
30 toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes

known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed
5 antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or
10 mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

Drug Screening

Further contemplated is the use of the polypeptides of the present invention, or
15 the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

20 This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic
25 or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

30 Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the

present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Polypeptides of the Invention Binding Peptides and Other Molecules

The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind polypeptides of the invention, and the polypeptide of the invention binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the polypeptides of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

This method comprises the steps of:

- a. contacting a polypeptide of the invention with a plurality of molecules; and
- b. identifying a molecule that binds the polypeptide of the invention.

The step of contacting the polypeptide of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate
5 immobilizing the polypeptide of the invention on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptide of the invention. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized polypeptide of the invention. The molecules having a selective affinity for the polypeptide of the
10 invention can then be purified by affinity selection. The nature of the solid support, process for attachment of the polypeptide of the invention to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

Alternatively, one may also separate a plurality of polypeptides into
15 substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant
20 phage). Individual isolates can then be "probed" by the polypeptide of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the polypeptide of the invention and the individual clone. Prior to contacting the polypeptide of the invention with each fraction comprising individual polypeptides, the polypeptides
25 could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for a polypeptide of the invention.
30 Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the polypeptide of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be

determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

5 In certain situations, it may be desirable to wash away any unbound polypeptide of the invention, or alternatively, unbound polypeptides, from a mixture of the polypeptide of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the polypeptide of the invention
10 or the plurality of polypeptides is bound to a solid support.

 The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind to a polypeptide of the invention. Many libraries are known in the art that can be used, e.g., chemically
15 synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, *Science* 251:767-773; Houghten et al., 1991, *Nature* 354:84-86; Lam et al., 1991, *Nature* 354:82-84; Medynski, 1994, *Bio/Technology* 12:709-710; Gallop et al., 1994, *J. Medicinal Chemistry* 37(9):1233-1251; Ohlmeyer
20 et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:10922-10926; Erb et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:11422-11426; Houghten et al., 1992, *Biotechniques* 13:412; Jayawickreme et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:1614-1618; Salmon et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, *Proc. Natl. Acad. Sci. USA* 89:5381-5383.

25 Examples of phage display libraries are described in Scott and Smith, 1990, *Science* 249:386-390; Devlin et al., 1990, *Science*, 249:404-406; Christian, R. B., et al., 1992, *J. Mol. Biol.* 227:711-718; Lenstra, 1992, *J. Immunol. Meth.* 152:149-157; Kay et al., 1993, *Gene* 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

30 In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:9022-9026.

By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide
5 functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list
10 benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

Non-peptide libraries can be classified broadly into two types: decorated
15 monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

Non-peptide oligomer libraries utilize a large number of monomers that are
20 assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer
25 libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of
30 peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, Science 249:386-390; Fowlkes et al., 1992; BioTechniques 13:422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89:5393-5397; Yu et al.,

1994, Cell 76:933-945; Staudt et al., 1988, Science 241:577-580; Bock et al., 1992, Nature 355:564-566; Tuerk et al., 1992, Proc. Natl. Acad. Sci. USA 89:6988-6992; Ellington et al., 1992, Nature 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, Science 263:671-673; and CT Publication No. WO 94/18318.

In a specific embodiment, screening to identify a molecule that binds a polypeptide of the invention can be carried out by contacting the library members with a polypeptide of the invention immobilized on a solid phase and harvesting those library members that bind to the polypeptide of the invention. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes et al., 1992, BioTechniques 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to a polypeptide of the invention.

Where the polypeptide of the invention binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

As mentioned above, in the case of a polypeptide of the invention binding

molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a polypeptide of the invention binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

The selected polypeptide of the invention binding polypeptide can be obtained by chemical synthesis or recombinant expression.

Antisense And Ribozyme (Antagonists)

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited clone. In one embodiment, antisense sequence is generated internally by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, Neurochem., 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research, 6:3073 (1979); Cooney et al., Science, 241:456 (1988); and Dervan et al., Science, 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoRI site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is

heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl₂, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding a polypeptide of the invention, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, *Nature*, 29:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell*, 22:787-797 (1980)), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.*, 78:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster et al., *Nature*, 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of interest. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA,

forming a stable duplex; in the case of double stranded antisense nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA sequence of the invention it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, *e.g.*, the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., *Nature*, 372:333-335 (1994). Thus, oligonucleotides complementary to either the 5' - or 3' - non- translated, non-coding regions of a polynucleotide sequence of the invention could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5' -, 3' - or coding region of mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556 (1989); Lemaitre et al., *Proc. Natl. Acad. Sci.*, 84:648-652 (1987); PCT Publication

NO: WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication NO: WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., *BioTechniques*, 6:958-976 (1988)) or intercalating agents. (See, e.g., Zon, *Pharm. Res.*, 5:539-549 (1988)). To this end,
5 the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil,
10 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine,
15 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil,
20 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose,
25 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl
30 phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded

hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., Nucl. Acids Res., 15:6625-6641 (1987)).

The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., Nucl. Acids Res., 15:6131-6148 (1987)), or a chimeric RNA-DNA analogue (Inoue et al., FEBS Lett. 5 215:327-330 (1987)).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. 10 (Nucl. Acids Res., 16:3209 (1988)), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., Proc. Natl. Acad. Sci. U.S.A., 85:7448-7451 (1988)), etc.

While antisense nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated 15 region are most preferred.

Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science, 247:1222-1225 (1990)). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs 20 corresponding to the polynucleotides of the invention, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5' -UG-3' . The construction and production of hammerhead ribozymes is well 25 known in the art and is described more fully in Haseloff and Gerlach, Nature, 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the polynucleotides of the invention; i.e., to 30 increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo.

DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

The antagonist/agonist may also be employed to treat, prevent, and/or diagnose the diseases described herein.

Thus, the invention provides a method of treating or preventing diseases, disorders, and/or conditions, including but not limited to the diseases, disorders, and/or conditions listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention

Other Activities

5 The polypeptide of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. These polypeptide may also be employed to stimulate angiogenesis and limb regeneration, as discussed
10 above.

 The polypeptide may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

15 The polypeptide of the present invention may also be employed stimulate neuronal growth and to treat, prevent, and/or diagnose neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. The polypeptide of the invention may have the ability to stimulate chondrocyte growth, therefore, they may
20 be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

 The polypeptide of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

 The polypeptide of the invention may also be employed for preventing hair
25 loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, the polypeptides of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

 The polypeptide of the invention may also be employed to maintain organs
30 before transplantation or for supporting cell culture of primary tissues.

 The polypeptide of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

5 The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, polypeptides or polynucleotides and/or agonist or antagonists of the present invention may be used to
10 modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive diseases,
15 disorders, and/or conditions), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used as a food additive or preservative, such as to increase or
20 decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated
25 nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of
30 positions beginning with the nucleotide at about the position of the 5' Nucleotide of

the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of
5 positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the
10 range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide
15 sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

20 A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X
25 in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under
30 stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization

conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1,
5 which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous
10 nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the
15 complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule
20 comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete
25 nucleotide sequence encoded by said human cDNA clone.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X
30 wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table

1; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

5 Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence
10 determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

 A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic
15 acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained
20 in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

 The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least
25 one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

 Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a
30 biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a

nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1;
and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA
Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit
Number shown for said cDNA clone in Table 1.

5 The method for diagnosing a pathological condition can comprise a step of
detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at
least two nucleotide sequences, wherein at least one sequence in said panel is at least
95% identical to a sequence of at least 50 contiguous nucleotides in a sequence
selected from said group.

10 Also preferred is a composition of matter comprising isolated nucleic acid
molecules wherein the nucleotide sequences of said nucleic acid molecules comprise
a panel of at least two nucleotide sequences, wherein at least one sequence in said
panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a
sequence selected from the group consisting of: a nucleotide sequence of SEQ ID
15 NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence
encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1
and contained in the deposit with the ATCC Deposit Number shown for said cDNA
clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA
molecules.

20 Also preferred is an isolated polypeptide comprising an amino acid sequence
at least 90% identical to a sequence of at least about 10 contiguous amino acids in the
amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

 Also preferred is a polypeptide, wherein said sequence of contiguous amino
acids is included in the amino acid sequence of SEQ ID NO:Y in the range of
25 positions beginning with the residue at about the position of the First Amino Acid of
the Secreted Portion and ending with the residue at about the Last Amino Acid of the
Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

 Also preferred is an isolated polypeptide comprising an amino acid sequence
at least 95% identical to a sequence of at least about 30 contiguous amino acids in the
30 amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid
5 sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human
10 cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in
15 Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA
20 clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human
25 cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1
30 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence

selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to
 5 increase the level of said protein activity in said individual.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit,
 10 goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

In specific embodiments of the invention, for each "Contig ID" listed in the fourth column of Table 6, preferably excluded are one or more polynucleotides
 15 comprising, or alternatively consisting of, a nucleotide sequence referenced in the fifth column of Table 6 and described by the general formula of a-b, whereas a and b are uniquely determined for the corresponding SEQ ID NO:X referred to in column 3 of Table 6. Further specific embodiments are directed to polynucleotide sequences excluding one, two, three, four, or more of the specific polynucleotide sequences
 20 referred to in the fifth column of Table 6. In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example. All references available through these accessions are hereby incorporated by reference in their entirety.

TABLE 6

Gene No.	cDNA Clone ID	NT SEQ ID NO: X	Contig ID	Public Accession Numbers
1	HSSDM23	11	904824	AI814485, AI872286, AI085288, AI871915, D55959, AI815039, AI863123, AI336860, H17328, AA044426, AA604984, AI633049, AW189982, AW025903, AL039802, AI620041, AW161698, F19322, AI357312, D54424, AW161017, D52832, F25495, AA703238, AI249687, C15890, R87515,

				H41877, D52711, AI910243, AA972364, AW002448, AI223172, H17356, AI419944, C15914, AA043060, AW137423, AA837263, D53580, AA285001, AA437366, AI884896, N62793, AI630922, AW139983, N93907, T06071, AI700165, AI934044, R87602, R90815, R87601, D80607, T23962, AA852308, AW393830, R90816, AA322589, AA330874, AI040803, F35183, AW393886, T12056, AI367549, D80888, AW204276, AA290964, AW389410, H50473, AW205735, AI356969, AI804924, AI619947, AW300654, AI948525, AI619622, AW050474, AI880215, AA224082, F34413, Z17406, F37450, AI540674, AW161156, AI797538, AW087199, AL047100, AI961414, AI254727, AI590043, AW051088, AW169671, AW162194, AI802542, AI352274, AI623941, AI624293, AI536685, AI859991, AI538885, AW020397, AI800473, AI538829, AW189716, AI621341, AI868931, AI890574, AI521594, AW088560, AA470491, AI241923, AI499963, AW105460, AW169784, AL036361, AI345778, AI285732, AI345543, AI521560, AI637584, AI927233, AI270183, AI271796, AI500714, AI684021, AW238688, AI687362, AI961589, C00462, AI918449, AL119863, AI587156, AI580214, AI470674, AI432969, AI583558, AA464646, AI636170, AI571439, AL110306, AI433157, AL036631, AI702073, AI687809, AI698391, AI567582, AI783504, AI929108, AL046466, AI281757, AI950892, AW151714, AL036673, AI609409, AI818353, AI434741, AI679266, AL121564, AI633125, AW059828, AI886181, AW303152, AI589428, AI538564, AI816884, AI915291, AI630252, AW152182, AW089275, AI973152, AI582932, AI433590, AI872423, AW129230, AI537677, AL037558, AI889189, AI435253, AI473536, AI610446, AW169618, AI318280, AI446023, AI866469, AI612913, AI961278, AI884318, AI452560, AI446046, AA641818, W74529, AA502794, AI537261, AI254042, AI587121, AW167918, AI612750, AW051044, AW008353, AI445992, AI581033, AI583578, AI696611, AI923370, AI355849, AI524654, AI288050, AL046618, AI932794, AI475371, AW080402, AI620284, AW163834, AI445990, AI827154, AI500061, AI473799, AL037030, AI866770, AI950729, AI539800, AI632408, AL040241, AW131999, AW152550, AW151136, AL046944, AI312428, AL138386, AI863191, AL039086, AI270295, AI335214, AI590120, AI473451, AI445611, AL119791, AL045500, AI670015, AI890907, AL043355, AI538637, AI267185, AI690687, AW161579, AL046595, AL040169, AI832245, AW149925, AC005815, AL137480, I48978, AF177401, AL117435, I89947, AF026008, AF017790, AL023657, I48979,
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2	HOFNX30	12	899523	AW270089, AB020686, and AL035701.
3	HLQFB12	13	899489	AA502331, AW444616, AI017393, AA568450, T85589, AA503839, T72043, T78178, T85588,

				AI699382, T86494, AA335186, AA299977, AA551860, AW079940, and AR027051.
4	HDPUM13	14	651321	AW007501, AA902287, AI858092, AI005351, AW083940, AI870864, AI032697, AW149115, AA829811, AA709070, AW264612, AA614344, AA643392, AI951841, AI312642, AA533443, AI799536, AA991955, AI830766, AA594172, AI289881, AW088660, AI276207, AW268666, AI741805, AI749660, AI369678, AI264768, AA625243, AI190367, AI816740, AI510691, AW168615, AI817506, AI792359, AW089929, AI609047, AI291890, AI268176, AA617718, AI394498, AI913963, F34379, AA985480, AI282722, AA864826, AI494152, AW050814, AI868440, AW129114, AA991995, AA937062, AA877343, AA737786, AI335628, AA335122, AI708280, AA318733, AA642608, AI245599, AI074177, AA603928, AW080143, AI768186, AA936631, AA569858, AA317892, AA995511, AI718073, AA345519, AI963480, AA318753, AI915027, AI291076, AA335136, AI830861, AI739187, AI340221, W87494, AI351218, AW054951, AI266613, AA779248, AI950591, T53694, AA335121, AW083985, AW148663, AA746624, R23643, AA804997, AA740560, AI749854, AA961830, AW168417, R35066, AA878942, AA983420, AA367958, T53693, AA804991, AI198965, AA862333, AA632062, AI828465, AW005612, AA729782, AA554005, AW080896, AI538203, H89138, AI918424, AA769697, AW084151, AI654137, AI540179, AI816976, AL045421, AA172258, AI817244, AI699175, AW020619, AA743358, AA587590, H95782, AI540606, AI865040, AW021662, AA767177, AI582822, AA811656, AW022593, AA824435, AL047172, AI913476, AW236186, AL118620, AI307557, AW084873, AW023928, AI376797, AI926593, AF135157, AF158248, AL049452, S70057, AL133049, X53587, X68560, AF130342, A15345, AL050170, AF131814, AR050959, AB026995, AF111851, AF150103, AF061573, AC006115, AL080074, AL096709, X79812, AF058921, A21625, X67813, AL133010, AF067223, AF113676, U80919, AC006112, AL080110, AF106697, AC004805, AL137539, AF067728, U66075, AF139986, AC002558, AF004162, AF211175, AF007142, AL133608, I48978, AF119336, A41575, AL133053, AF094480, AF107018, A57389, AL133088, E01357, AL133016, S68736, AF137367, E01314, AF098162, M79462, AF192522, AF161413, AL022165, A86558, S36676, D44497, AL080154, X51694, AF039202, AF126372, I80062, X60769, X76228, X99257, AJ006039, AL137284, X68249, Y00093, E15568, AC005156, AF179633, X98066, Y11254, A83556, AF199509, X66113, E13998, AL137641, and S69510.

4	HPLAT62	44	839292	<p> AW007501, AA902287, AI858092, AI005351, AW083940, AI870864, AI032697, AA829811, AA709070, AW264612, AA643392, AI951841, AW149115, AI312642, AA614344, AA533443, AI799536, AA991955, AI830766, AA594172, AI289881, AI741805, AI276207, AW088660, AW268666, AI749660, AI369678, AI264768, AA625243, AI190367, AI816740, AI510691, AW168615, AI817506, AI792359, AI291890, AW089929, AI268176, AI609047, AA617718, AI913963, F34379, AA985480, AI282722, AI394498, AA864826, AW050814, AI494152, AI868440, AA991995, AA937062, AW129114, AA877343, AI335628, AA335122, AA737786, AI708280, AA642608, AA318733, AI245599, AW054951, AA603928, AI074177, AA936631, AA569858, AW080143, AI768186, AA995511, AA317892, AI718073, AA345519, AI915027, AI963480, AA318753, AW083985, AI291076, AA335136, AI340221, W87494, AI739187, AI830861, AI351218, AI266613, AA779248, T53694, AA335121, AI950591, AA746624, R23643, AA804997, AA740560, AI749854, AW148663, AA961830, R35066, AW168417, AI299182, AA878942, AA983420, AA367958, T53693, AA804991, AI198965, AI913330, AA862333, AA632062, AI590043, AI887775, AI500714, AW089557, AL039390, AI433157, AI648567, AI554821, AW151136, AI539771, AL045626, AI274759, AI537677, AI494201, AI500659, AI866465, AI815232, AI801325, AI500523, AI538850, AI582932, AI872423, AI284517, AI923989, AI500706, AI491710, AI445237, AI491776, AW151138, AI889189, AI521560, AI500662, AI539800, AW172723, AI284509, AI538885, AI889168, AI440263, AI866573, AI633493, AI434256, AI866469, AI434242, AI805769, AI888661, AI284513, AI888118, AI570169, AI436429, AI859991, AI889147, AI355779, AI371228, AI581033, AI440252, AL047422, AI866786, AI860003, AI610557, AI242736, AI828574, AI887499, AI539781, AI539707, AI559957, AI521571, AI281867, AI620284, AI345416, AI345612, AI582912, AI671642, AI345415, AI866461, AL079960, AI623736, AI469775, AI866820, AL045500, AL045421, AI433976, AI890907, AI355008, AI273179, AI371251, AI866510, AI923046, AI950664, AI335426, AI348777, AW151979, AI885949, AW302924, AI690946, AI249946, AI366900, AI432644, AW105601, AI285419, AL047187, AL042488, AW191003, AI922550, AW023590, AW197139, H89138, AL048375, AI364788, AW129230, AW169604, AI432666, AI866581, AW005612, AA641818, AI815150, AI275175, AI633125, AI499463, AW073697, AL046942, AI670009, AI610362, </p>
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4	HE6DI14	45	361400	AW007501, AA902287, AI858092, AI005351, AW083940, AI870864, AI032697, AA829811, AW264612, AA709070, AA614344, AA643392, AI951841, AW149115, AI312642, AA533443, AI799536, AA991955, AI830766, AA594172, AI289881, AI741805, AI276207, AW088660, AW268666, AI749660, AI369678, AI816740, AA625243, AI264768, AI190367, AI510691, AW168615, AI817506, AI792359, AI291890, AW089929, AI268176, AI609047, AA617718, AI913963, F34379, AI282722, AI394498, AA985480, AA864826, AI494152, AW050814, AI868440, AW129114, AA991995, AA937062, AA877343, AA335122, AI335628, AA737786, AI708280, AA642608, AA318733, AW054951, AI245599, AA603928, AI074177, AW080143, AA936631, AA569858, AI768186, AA995511, AA317892, AI718073, AA345519, AI915027, AI963480, AA318753, AI291076, AA335136, AI340221, W87494, AI739187, AI830861, AI351218, AA779248, AI266613, T53694, AA335121, AI950591, AW083985, AW148663, AA746624, R23643, AA804997, AA740560, AI749854, AA961830, R35066, AW168417, AA878942, AA983420, AA367958, T53693, AA804991, AI198965, AA862333, AA632062, AI557082, AI541321, AI541205, AI557808, AI557238, T18597, D51002, AI557258, AI525856, AI557602, AI541027, AI557731, AW023469, AI525500, AW020592, AI557533, AI540890, AW020328, AW022874, AI541048, AI535660, AI828465, AI525556, AW021693, AI557426, AI557222, AI557241, AW023351, AW022593, AW022981, AW021182, AW023863, AW021178, AW022826, AI557697, AI557285, AI526078, AW020397, AW022456, AW020480, AI525656, AI541346, AW019988, H65400, AI557084, AW023617, AW020425, AW021561, AW020543, AW022299, AW080896, AW022571, AW411235, AW021466, AW022727, AI557234, AW021059, AI541056, AI525669, AW020931, AW022308, AW411265, AW410902, AA729782, D50992, AI557041, Z32887, AW020406, AL045453, AW411351, AW020295, AI612885, AI557262, Z33559, AW005612, AI469764, AW189802, AI654137, AI540179, AA554005, AW411043, AW023884, D59751, AW020634, AW020629, AW021717, AW265004, AI699175, AW022760, AA127565, AI535639, AA743358, AA259207, H95782, AA769697, AF135157, AR050070, S68736, A62298, Y08991, A91160, AF158248,

				<p>A82595, A82593, Z30183, U94592, Y11505, S73498, AL133049, E12888, AL049452, S70057, AR030544, E12579, A62300, A15345, S71381, X53587, D44497, A93016, AC004213, AF111851, AF061573, AF130342, AF006072, AR068753, AR050959, AR068751, Y11254, AF065135, A76337, A76335, I92592, U80919, AL050170, AF131814, AL080110, AF150103, AR038854, L40386, A21625, AF139986, I48978, AB026995, A41575, AF094480, AF067223, AC004399, AC006115, AF192522, AF161413, AL080074, AL137539, E01314, A86558, S36676, AF067728, X79812, AL133053, AF058921, AF004162, X67813, AL133010, AF107018, AC005156, I80062, AF211175, AF113676, AC006112, X98066, AF106697, U45328, E01357, AL133016, AF098162, M79462, AF141976, AL110221, AL080154, X51694, AF007142, AF039202, AL137574, AF124396, AL137641, AC005209, I48979, X60769, X76228, A41579, X99257, AL137560, E03168, AL133607, AJ006039, L12407, AL137284, X66113, AL133608, J05277, AL022165, AC004554, AF119336, A83556, AF199509, AF044323, E13998, S82852, AF081825, X82434, and A57389.</p>
4	HACBG19	46	1050384	<p>AW007501, AA902287, AI858092, AI005351, AW083940, AI032697, AI870864, AW149115, AA829811, AA709070, AW264612, AI951841, AA643392, AA614344, AI312642, AA533443, AI799536, AA991955, AI830766, AA594172, AI289881, AI741805, AI276207, AW088660, AW268666, AI749660, AI369678, AI264768, AA625243, AI816740, AI190367, AI510691, AW168615, AI817506, AI291890, AW089929, AI268176, AI792359, AA617718, AI913963, F34379, AA985480, AI282722, AA864826, AW050814, AI868440, AA991995, AA937062, AI494152, AA877343, AA737786, AI609047, AW129114, AI394498, AI335628, AA335122, AI708280, AA642608, AA318733, AI245599, AA603928, AA936631, AW054951, AA995511, AA317892, AI718073, AA569858, AI915027, AI768186, AI963480, AA318753, AW080143, AI291076, AA335136, AI340221, W87494, AI830861, AI351218, AI266613, AA779248, T53694, AA335121, AI950591, AA746624, R23643, AA804997, AA740560, AI749854, AA961830, AA345519, R35066, AA878942, AI739187, AA983420, AA367958, T53693, AA804991, AI198965, AA862333, AA632062, AI828465, AA078636, AI557262, AI541205, AI525556, AI557082, AI557602, AI535828, AI541075, AI557084, AI557474, AI557809, AI541034, AI557258, AI541321, AI546829, AI541346, and AF135157.</p>
4	HACBG19	47	1050383	<p>AW007501, AA902287, AI858092, AI005351, AW083940, AI870864, AI032697, AA829811,</p>

				AA709070, AW264612, AA643392, AI951841, AW149115, AI312642, AA614344, AA533443, AI799536, AA991955, AI830766, AA594172, AI289881, AI741805, AI276207, AW088660, AW268666, AI749660, AI369678, AI264768, AA625243, AI190367, AI816740, AI510691, AW168615, AI817506, AI792359, AI291890, AW089929, AI268176, AI609047, AA617718, AI913963, F34379, AA985480, AI282722, AI394498, AA864826, AW050814, AI494152, AI868440, AA991995, AA937062, AW129114, AA877343, AI335628, AA335122, AA737786, AI708280, AA642608, AA318733, AI245599, AW054951, AA603928, AI074177, AA936631, AA569858, AW080143, AI768186, AA995511, AA317892, AI718073, AA345519, AI915027, AI963480, AA318753, AI291076, AA335136, AI340221, W87494, AI739187, AI830861, AI351218, AI266613, AA779248, T53694, AA335121, AI950591, AA746624, AW083985, AW148663, R23643, AA804997, AA740560, AI749854, AA961830, R35066, AW168417, AA878942, AA983420, AA367958, T53693, AA804991, AI198965, AA862333, AA632062, AI557082, AI541321, AI541205, AI557808, AI557238, T18597, D51002, AI557258, AI557602, AI525856, AI541027, AI557731, AW023469, AI525500, AW020592, AI557533, AI540890, AI541048, AI828465, AI535660, AW020328, AW022874, AW022593, AI525556, AW021693, AI557426, AI557222, AI557241, AW023351, AW022981, AW021182, AW023863, AW021178, AW022826, AI557697, AI557285, AI526078, AW020397, AW022456, AW020480, AI525656, AW023617, AI557084, AI541346, AW019988, H65400, AW020425, AW021561, AW020543, AW022299, AW022571, AW411235, AW021466, AW022727, AI557234, AW021059, AI541056, AI525669, AW020931, AW022308, AW411265, AW410902, AA729782, D50992, Z32887, AW020406, AW080896, AA554005, AW411351, AW020295, AW022760, AI612885, AI557262, Z33559, AW189802, AI557041, AW411043, AW023884, D59751, AW020634, AI538203, AW020629, AW021717, H89138, AW265004, AL045453, AA127565, AI535639, AA259207, AI918424, AA769697, AA100772, AW264964, AF135157, AR050070, S68736, A62298, Y08991, A91160, AF158248, A82595, A82593, Z30183, S73498, Y11505, U94592, AL049452, S70057, E12888, AL133049, AR030544, E12579, X53587, A62300, D44497, S71381, X68560, AF130342, A93016, AC004213, A15345, AL050170, AF006072, AF131814, AR068753, AR050959, AR068751, AB026995, Y11254, AF065135, A76337, A76335, I92592, AF111851, AF150103, AF061573, AC004399, AC006115, L40386,
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				A21625, AL080074, AL096709, X79812, AF058921, X67813, AL133010, AF107018, AF113676, U80919, AC006112, AF067223, AL080110, AF106697, AL137539, AF067728, AL133053, U66075, AF139986, AC005156, AF211175, AF007142, AF004162, AL133608, AC004554, I48978, AF119336, A41575, AF094480, U45328, A57389, AL133088, E01357, AL133016, AF137367, AF098162, M79462, AF192522, AF161413, AL022165, AF141976, A86558, S36676, AL080154, X51694, E01314, AF039202, AF126372, AC005209, I80062, X60769, X76228, AL031295, X99257, A59344, AJ006039, L12407, AL137284, X68249, J05277, Y00093, E15568, and AF179633.
4	HAPQT56	48	902207	AW007501, AA902287, AI858092, AI005351, AW083940, AI870864, AI032697, AW149115, AA829811, AA709070, AW264612, AA643392, AI951841, AA614344, AI312642, AA533443, AI799536, AA991955, AI830766, AA594172, AI289881, AI741805, AI276207, AW088660, AW268666, AI749660, AI369678, AI264768, AA625243, AI816740, AI190367, AI510691, AW168615, AI817506, AI792359, AI291890, AW089929, AI268176, AA617718, AI609047, AI913963, F34379, AA985480, AI282722, AI394498, AA864826, AW050814, AI494152, AI868440, AA991995, AA937062, AW129114, AA877343, AI335628, AA335122, AA737786, AI708280, AA642608, AA318733, AI245599, AW054951, AA603928, AI074177, AA936631, AA569858, AW080143, AI768186, AA995511, AA317892, AI718073, AA345519, AI915027, AI963480, AA318753, AI291076, AA335136, AI340221, W87494, AI739187, AI830861, AI351218, AI266613, AA779248, T53694, AA335121, AI950591, AW083985, AA746624, AW148663, R23643, AA804997, AA740560, AI749854, AA961830, R35066, AW168417, AA878942, AA983420, AA367958, T53693, AA804991, AI198965, AA862333, AA632062, AI557082, AI541321, AI541205, AI557808, AI557238, D51002, AI557258, AI525653, AI541027, AI557731, AI557602, AI525856, AW020592, AI525500, T18597, AI541048, AW021693, AI557533, AI540890, AI828465, AW022874, AI535660, AA585439, AI557426, AI557222, AI557241, AW023351, AW023469, AI525556, AW022981, AW021182, AW021561, AW023863, AW021178, AW022826, AI305283, AW020397, AW022593, AW020480, AW020328, AI557697, AI525656, AI583584, AW019988, AI557285, AI525499, AI526078, AW020931, AW022571, AW022456, AW020425, AW022760, AI557084, AW022299, AI541346, H65400, AW411235, AW021059, AI541056, AI525669, AW411265, AW410902, AW023884, AA729782,

				<p>AW020543, AW020406, AA554005, AW022727, AI557234, AW022308, AL138459, AW023617, AW411351, AW020295, AI612885, AW189802, D50992, AW411043, Z32887, AI273179, AW020629, AW021717, H89138, AW265004, AW411337, AW021466, AA127565, AA259207, AW084151, AL121328, AA100772, AW264964, AI557262, AW020876, AI673184, Z33559, AF135157, S68736, AR050070, A62298, Y08991, A91160, AF158248, E12888, AL133049, A82595, A82593, Z30183, U94592, AL049452, Y11505, S70057, AF107847, E12579, X53587, X96757, S73498, AF130342, A62300, A93016, AC004213, A15345, X68560, U45328, AL122049, AL022165, A18777, AF131814, D44497, AR068753, AL137548, AR050959, AR068751, AB026995, Y11254, AF065135, A76337, A76335, I92592, AC006115, AL050170, AF111851, AF150103, AF061573, AF006072, U67813, A21625, AL080074, X79812, AF058921, X67813, AL133010, AL133014, S71381, AF113676, AR030544, U80919, AF141976, AC006112, L40386, AL080110, D00174, AF106697, AL137539, AF067728, AF139986, AF169202, S65585, AP000081, AL096709, AF211175, A59344, AF007142, AL080150, AF029728, AF004162, I48978, AR005195, AL133608, AF072933, AF119336, A41575, AL133053, AF153205, AF094480, AL080129, AF067223, Y08769, A57389, AL133088, AF030165, AL133016, AF137367, AF098162, M79462, AF192522, AF161413, Z93784, AF022813, E01314, A86558, S36676, AL137562, AL080154, AF039202, U66075, AL137665, AF126372, AB014082, AP000514, AC006203, U69730, I80062, Y17327, X60769, X76228, X99257, AJ006039, AL137284, AL137534, J05277, Y00093, E15568, AF179633, X98066, A83556, M85165, AF082324, AF199509, AL137641, and AL050322.</p>
4	HLYAN43	49	513179	<p>AA449296, AA449556, AI524150, AI984842, AI609927, AI819436, AW009733, AA465450, AI948444, AI277802, R41061, AI672999, AI056173, AI557436, AI277801, AI189314, AI581709, AA954708, AA683571, AA933818, AW079525, AI078401, AA379775, AA369058, AI634327, AA742493, AI950621, AI365075, AA663732, AA877647, AA862700, AA877471, AI391456, AW089003, R18095, AI566394, AA912462, AI301746, AA028143, AW102581, AI914810, AA737984, AA369057, H83569, AI376709, AA028180, AA969789, AI889818, AI446023, AI590043, AI524179, AA916033, AW182790, AI590686, AI744985, AI950729, AI627866, AA761557, AW195943, AW024594, AW163834, AI498067, AI373276, AI866624, AL138457, AA676361, AI472536, AI932739,</p>

				<p> AW089844, AW194014, AW130356, AI689470, AA767177, AW081383, AI345415, AI653402, AW080992, AI401697, AW080290, AI673301, AI922543, AW193288, AI799313, AI933574, AI288050, AI688858, AI638644, AI381676, AW051088, AI890907, AI565048, AA743430, W45039, AI952145, AI693016, AI357599, AI539800, AI763414, AW191844, AI174394, AI633198, AI932794, AI673297, AI499570, AI584140, AL047100, AI338427, AI282688, AI365256, AI609556, AI499963, AI474146, AW262557, AI522052, AI637584, AI583578, AW089006, AI619691, AW198090, AI922561, AI432969, AI872423, AI696583, AI864836, AI677646, AI620944, AI973152, AI434468, AI571980, AI583584, AI633300, AI146568, AI671673, AI872472, AA835966, AI961414, N25033, AW008226, AI673363, AI624154, AW078606, AW081298, AW083572, AI933903, AI590755, AI367328, AI422080, AL040449, AI798351, AI500061, AI440399, AW084233, AI633125, AI473799, AA587590, AI690813, AI619426, AI658566, AI783504, AI927233, AI367705, AI922707, AW088691, AI479292, AI571439, AI559752, AI802244, AI245008, AI624693, AI609360, AI972944, AI521100, AW129264, AI678602, AI554411, AI553645, AI799189, AI762707, AI350880, AI537967, AI669612, AI800648, AI824576, AW088560, AW075382, AI263584, AI954095, AI345612, AW029238, AI866691, AI096613, AI279628, AI863047, AI679069, AI345416, AW025279, AI570056, AI681985, AI434731, AI683270, AI651840, AI678446, AW075305, AW078777, T69241, AW196720, AW166979, AI589428, AW085786, AA502794, AA831948, AI679778, AI538686, AA514684, AI284484, AI343582, AI440238, AI961310, AI611810, AI811603, AI860817, AW080076, AW150578, AI887381, AI539260, AI536563, AI559596, AW055081, AI633061, AI680066, AW026477, AI274655, AI889306, AI356868, R41605, AI582932, AW082532, AI689614, AI362537, AA743385, AW151714, AI687362, AL137554, AF090903, D83032, Y14314, AR059883, X63162, AI5345, AC005992, I22272, AF183393, AL080110, AF113694, AL122049, AL137560, AF107847, S77771, AL050143, AL117443, AF061981, AL137550, AR038854, AL031984, AL137463, Z72491, A18777, E12747, A77033, A77035, AF153205, AL050138, AL049452, X98066, AL137530, AL133062, AL110228, AL137527, Z97214, AF169154, X80340, AF031147, AF161413, AL133623, E12579, AL080140, AL133619, AL137292, AR029490, U90884, AL049460, U37359, A45787, E12580, A08913, I89947, A52563, X53587, L19437, AF159615, </p>
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				AF094480, AL133557, AL080139, AL137574, AL133075, AL050149, A08912, U49434, AL080150, AL133608, U79523, AF032666, A08910, A08911, A08909, X66871, Z13966, AL080154, AL110226, AL137294, AF057300, AF057299, AR029580, A08907, I48978, A08908, AR068466, S76508, AC004227, A32826, A30330, A32827, A30331, AL133084, AB026995, U89906, AL080159, X84990, AB007812, AL080158, AL137533, I32738, Z48796, U75378, X81464, AF054986, AR009628, AF115392, X92070, AF047716, X57084, AL133568, A27171, AL133049, AL137548, AL137665, AF000145, A18788, E02152, AF091084, AB016226, AL133637, AL122050, A76337, E02349, AL110296, AF079763, AF017790, M27260, I26207, AF205861, I09499, U78525, AL137268, AF008439, AR036183, AL137300, AR068751, AF067728, L13297, E07108, AF177401, AF044323, X67813, AL110224, AL050393, AL137662, AJ012755, AL137471, S54890, A21103, AF090900, AL133069, E03348, AF028823, A86558, A41575, AL117435, AL137562, E03349, AL110221, AF090896, Z82022, U95738, AF026816, I41145, AF022813, AL096709, AF215669, AL137478, U83980, X89102, AL117416, E00984, I04527, AL050116, AJ003118, AL080148, AF043642, AF115410, AF077051, A65965, X63410, AL137627, A92311, X82434, AF114170, AF131773, AL133558, Y11587, U76419, AL133070, A76335, AF141289, AL050172, AF200464, AL133624, E01314, U83172, AF199027, A65943, AF030513, AL049466, AL110222, AJ005690, AF098162, AL137539, AF003737, Y10823, AL137557, A65340, X62580, AF200416, AL137538, AF061795, AF151685, S82852, AF180525, AF019298, X87224, AC002467, AC002464, M84133, E01573, E02319, AF106945, AL096728, AL080146, Y13350, AF114784, I17544, AF106697, U42031, AF199509, AF036268, AB028451, and AL137273.
5	HTLGV19	15	901886	AI392811, AI302099, AA478198, AI435141, AI803046, AI928295, AA478040, AI928292, AW206706, AW367708, and AA846117.
6	HTTCT46	16	423038	AW014933, AW021164, AW020116, AI453569, AW338670, AI424992, AI922706, AI742885, AI521511, AI342112, AI342123, AA864962, AI916681, N48528, AI813984, AI570185, H30104, AW305161, AI088387, D62133, N69067, D62597, AW020789, AA977334, AI745211, N67892, AW262786, N63231, W56148, N39415, AI093708, AA904959, D61737, D62236, AI218410, W06903, AI280284, AI287305, AA227767, N91349, N69076, N67939, AA227951, AI381291, W39563, D62569, D62771, D62982, AW264446, AA045327, W20008, D62028, AW263349, AA889218,

				<p>W15431, AA332364, AA774515, H30466, AA219100, AI263713, N75186, AI394180, AW104259, AI700865, AI537351, D62862, AI926000, D54372, D61808, AI261756, D62929, D62584, H88893, AA861328, D62870, D62749, AW022422, AW023728, AA358198, D62922, D62565, D62880, AW026876, AA219099, N22301, AA367442, H88894, D62754, D62519, D62119, H30183, D62912, D79392, AA781602, AA295227, D79802, H88966, H88940, H90645, D61934, AA329940, D62847, D62721, D79695, D62811, AW339960, AI610487, H89049, D63133, AA625257, D61880, H89169, D62813, AA045385, D79492, D79678, AA327731, D62551, AA243742, AA708797, AA328664, D79421, D63063, D63015, AA193444, D61758, D79830, H91568, D62382, AW020090, AI934365, D62456, D62755, D62809, D79356, AI127717, D62911, D62707, D79638, W21015, D62685, D79491, AW262616, D62836, D61876, D79741, AA329804, N89676, D79241, D61920, N67575, H27453, D79609, AA296367, D62256, D79293, R06414, D62973, AA249597, D79825, D79456, D79904, AA903304, D62958, D79460, D61750, D62080, T97739, N66456, R06469, AW244004, AI040141, T97846, C16149, AA332194, AI270264, AW302407, AW023330, N56025, AW361429, AL133114, AL110267, AF100758, AF192483, M37974, AF017339, AF105150, D31951, AF088023, AF112465, AF192478, AF192481, AF192480, AF192482, AF192479, and AF192477.</p>
6	HSDEE58	50	905256	<p>AW014933, AW021164, AW020116, AI453569, AW338670, AI424992, AI922706, AI742885, AI521511, AI342112, AI342123, AA864962, AI916681, N48528, AI813984, AI570185, H30104, AW305161, AI088387, D62133, N69067, AW020789, D62597, AA977334, AI745211, N67892, AW262786, N63231, W56148, N39415, AI093708, AA904959, D61737, D62236, AI218410, W06903, AI280284, AA227767, AI287305, N91349, N69076, N67939, AI381291, AA227951, W39563, D62569, D62771, D62982, AW264446, W20008, AA045327, D62028, AW263349, AA889218, W15431, AA332364, AA774515, H30466, AA219100, AI263713, N75186, AI394180, AW104259, AI700865, AI537351, D62862, D54372, AI926000, D61808, AI261756, D62929, D62584, H88893, AA861328, D62870, D62749, AW022422, AW023728, D62922, D62565, AA358198, D62880, AW026876, AA219099, N22301, AA367442, H88894, D62754, D62519, D62119, H30183, D62912, D79392, AA781602, AA295227, D79802, H88966, AI934365, H88940, H90645, D61934, AA329940, D62847, D62721, D79695, D62811, AW339960, AI610487, H89049, D63133, AA625257, D61880, H89169, D62813, AA045385, D79492, D79678,</p>

				AA327731, D62551, AA243742, AA708797, AA328664, D79421, D63063, D63015, AA193444, D61758, D79830, H91568, D62382, AW020090, D62456, D62755, D62809, D79356, AI127717, D62911, D62707, D79638, W21015, D62685, D79491, AW262616, D62836, D61876, D79741, AA329804, N89676, D79241, D61920, N67575, H27453, D79609, AA296367, D62256, D79293, R06414, D62973, AA249597, D79825, D79456, D79904, AA903304, D62958, D79460, D61750, D62080, T97739, N66456, R06469, AW244004, AI040141, T97846, C16149, AA332194, AI270264, AW302407, N56025, AW023330, AW361429, AL133114, AL110267, AF100758, AF192483, M37974, AF017339, AF105150, D31951, AF088023, AF112465, AF192478, AF192481, AF192480, AF192482, AF192479, AF192477, and D79422.
8	HOHCA60	18	906064	AI917724, AI342006, AI261611, AI750970, N33407, AI825646, AA482392, AI459225, W47029, AA971699, N44869, W47220, AA284278, AI905640, AI905601, AI005408, AI806281, and AW137913.
8	HOHCA60	52	906419	AI608789, AA411541, AW150272, AI991149, AI934755, AI763268, AI090866, AA464314, AI277953, AI624414, AI954973, AI167471, W96217, AI675874, AA604659, W93790, AW016493, AA813712, AW082293, AI159950, AI038163, AA834939, AI279359, AA297727, AW004853, AA297726, AA550765, H91883, AA456486, W96311, T16058, T36190, AA412342, AA382771, AA412452, AA781072, AA377166, AA344749, Z38920, AA369026, AA326408, AA341054, R41523, AI435982, AW016126, R18534, AA477934, AA664345, AI144001, AA722624, AA628669, W93789, Z42768, D45660, T52089, H06991, AL080162, AF097484, AF056183, AC005089, AF097485, and AF097523.
8	HOHCA60	53	904949	AI917724, AI342006, AI261611, N33407, AI825646, AA482392, W47029, AI750970, N44869, W47220, AI459225, AA284278, AA971699, AI905640, AI905601, and AW137913.
8	HOHCA60	54	904948	AA482392, AI459225, AA971699, and AW137913.
9	HLQFT18	19	899439	AA502331, AA503839, AW444616, AI699382, AA568450, AI017393, T72043, T85589, T78178, T85588, AA299977, T86494, AA335186, AA551860, AI421755, AA525331, AW019964, AI567391, AA558404, AI671077, AI279417, T95676, AI200649, AA828730, AA586433, AI821273, T51743, AI355246, H43183, AI923052, AI565084, AA524616, AA371410, AW166641, AA937809, AA482792, AA904211, AI049676, AA630854, H65213, AA834799, R93919, AW023111, AI267356, AL041375, AA658934, AA304858, AI831172, T84567, AW265688, AI280266, AL138431, AA515939, AA349937,

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12	HAGDA35	22	1070597	AI685285, AA648924, AA215679, AI241084, AA279477, AA810583, AI885510, AA769118, AA810311, W47115, AA662537, AL022165, AL050307, and AA278532.
12	HAGDA35	57	618529	AA278194, AW297646, AA279477, W47116, W47115, AA662537, T05300, AA832156, and AL022165.
12	HAGDA35	58	637487	AA278194, AW297646, AA279477, W47116, W47115, AA662537, T05300, AA832156, and AL022165.
13	HRODQ04	23	777923	AI065139, AI686204, AI766943, AI623280, AA425583, AI678169, AA425387, AI032814, AI220994, AA595016, AI240411, AI758161, AA132163, AI271565, AI332512, AA451730, AI393086, AI961133, AA135504, AA424150, AA468862, AA135505, H12316, AW299404, AW207017, AA132078, AA318401, AI474190, AA375142, AW069070, AI381324, AA552888, AI373040, AI905235, AW138311, AI816870, D80045, C14331, C14429, D59275, D80253, C14389, D80227, D59467, D51799, D80195, D59502, D80164, D80366, D80269, D58283, D80166, D51423, D59619, D80210, D80391, D80240, D80043, D80038, D59859, D80212, D80193, D80196, D80188, D80022, C15076, D80219, D59927, D81030, D57483, D51060, D80024, D59610, AW366296, D50979, D59889, D59787, D80378, D50995, AW177440, AA305409, D80241, C14014, C75259, T03269, AA514188, D51022, AA305578, AW178893, D81026, D80251, C14407, AW179328, D80248, D80134, AA514186, AW378532, AW360811, D80522, D51250, AW178775, D80133, AW177501, AW177511, AW369651, D52291, F13647, AW375405, AW178762, AW378540, D58253, D59695, AW352158, D80168, AW377671, AW360844, D80268, AI535686, AW360817, AW375406, AW378534, AW179332, AW377672, AW179023, AW178905, C05695, AW352117, C14227, AW176467, C06015, D80302, AI910186, D81111, AI905856, D80132, AW352171, D80439, AW377676, AW178906, AW352170, AW177731, C14298, AW178907, AW179019, AW179024, D80247, D80064, Z21582, AW177505, AW360841, AW179020, AW178909, D59373, AW177456, AW179329, AW178980, AW177733, AW378528, AW178908, AW178754, AW179018, AW352174, AI557751, D51103, T48593, AA809122, AW179004, AW179012, AW178914, AW378525, AW360834, D80157, T11417, AW177722, AW367967, AW177728, D51097,

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14	HDPOL27	24	1163002	AI936172, AI341137, AI635373, AI650516, AA496235, AA993067, AW140139, AA496236, AI823907, AA534789, AI694980, AI337223, AI493181, AA649205, AI337224, AI246486, AA478751, AA479971, AA421603, AI744621, AW194078, H28871, H22744, AA516280, R26128, R72261, R25510, R45574, W20038, R62652, M86047, AA381555, AA381682, AA381593, AI572487, AA381497, R26340, AA057695, AA057610, AA381478, H47862, AI014588, AI675309, AW277012, AI288285, AW263796, AA806757, AW151132, AW090498, AI804586, AA908294, AI590043, AI440210, AW025279, AI537516, AI628325, AW162194, AI370623, AI401697, AI669864, AI148256, AI421252, AW081866, AI978703, AI493836, AI818353, AI004911, AW074172, AI285439, AI289791, AI624520, AA749425, AI886355, AA088789, AW008166, AI918637, AI491710, AI538342, AW085786, AI500714, AI433611, AI348901, AA514684, AI738762, AI452876, AA835966, N25033, AI095113, AI539800, AI469516, AA904121, AA575874, AW168875, AI917994, AI434656, AW026707, AI655932, AI658566, AI697178, AI471429, AI590755, AW088793, AW169671, AL039716, AI624154, AI075885, AI859310, AI417790, AI610086, AI963846, AW027898, AI912297, AI926593, AL044725, AW076124, AI245008, AI689096, AI524652,

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14	HDPOL27	59	637587	AI936172, AI341137, AI635373, AI650516, AA496235, AA993067, AW140139, AI823907, AA534789, AI694980, AI337223, AI493181, AA649205, AI337224, AI246486, AA478751, AA479971, AA421603, AW194078, H28871, H22744, AA516280, R26128, R72261, R25510, R45574, R62652, W20038, AA381555, M86047, AA381682, AI572487, AA381593, AA381497, R26340, AA057695, AA057610, AI744621, AA381478, AA496236, AI014588, H47862, AI675309, AW277012, AL050267, AF228421, U15635, and AF147427.
14	HEBCV31	60	469522	AI936172, AI635373, AI650516, AA993067, AA496235, AW140139, AI823907, AA534789, AI694980, AI493181, AA479971, AA421603, AW194078, AI337223, AI246486, H28871, AI341137, AI337224, H22744, AA516280, AA649205, R26128, R72261, R45574, R62652, AI572487, R26340, AA057695, AA057610, AI014588, AA478751, AI288285, N75771, AW263796, AW090498, N71180, AA806757, AW151132, AI804586, AA908294, AI590043, AI440210, AW025279, AI537516, AI628325, AW162194, AI370623, AI401697, AI669864, AI148256, AI421252, AW081866, AI978703,

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16	HKGDP17	26	899502	AI804162, AI340667, AI038755, AW150209, AF108083, AC005486, AC005969, Z98946, AC006160, AL031255, AC007216, AF003529, U95742, and AC005291.
17	HSVBD67	27	905861	AI814485, AI872286, AI085288, AI871915, D55959, AI815039, AI863123, H17328, AI336860, AA044426, AA604984, AW189982, AI633049, AW025903, AL039802, AI620041, AW161698, F19322, AI357312, D54424, D52832, AW161017, F25495, AA703238, AI249687, C15890, R87515, H41877, AI910243, D52711, AA972364, AW002448, AI223172, H17356, AW137423, AA043060, C15914, AA837263, D53580, AI419944, AA285001, AA437366, AI884896, N62793, AI630922, AW139983, N93907, T06071, AI700165, R87602, AI934044, R90815, R87601, D80607, T23962, AA322589, AA852308, AW393830, R90816, AA330874, AI040803, F35183, AW393886, T12056, AI367549, AW204276, D80888, AA290964, AW389410, H50473, AW205735, AI356969, AI804924, AI619947, AW300654, AI948525, AI619622, AW050474, AA224082, AI880215, F34413, Z17406, C00462, AL119457, AL119324, AW392670, AL134524, AW084080, AL119443, AL119391, AL119484, AL119444, U46347, AL134527, AL119319, U46350, AL119439, U46351, AL119522, AI499335, AL119418, AL134528, AW372827, AW363220, AL119363, Z99396, AL119497, AL037205, U46341, AI586959, AW384394, AL119341, AL119396, AL134531, AW148743, AL119401, AR060234, AB026436, AR066494, AR054110, A81671, and AR069079.
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19	HFCEQ37	29	746860	AW297465, R37473, R20618, H08151, H09566, H11386, R60580, H05295, Z40466, AA013396, H24061, R44488, Z39576, R60633, AA885521, AA812965, F03288, R49325, F03287, T17067, H05345, Z44590, F05379, F05979, R40430, R21026, F05378, R11881, AI500061, AI927233, AI621341, AI521596, AI888317, AI610446, AI289791, AI432570, AI561170, AI537273, AI539260, AI440238, AI553645, AI624693, AI888575, AI866503, AI696603, AI571439, AI433157, AI648567, AI690946, AI554821, AW151136, AI539771, AI432644, AI537677, AI494201, AI567971, AI500659, AI909697, AI866465, AI815232, AI801325, AI500523, AI417790, AI538850, AI285439, AI887775, AI582932, AI590043, AI872423, AI923989, AI284517, AI500706, AI491776, AI445237, AW151138, AI889189, AI521560, AI500662, AI539800, AW172723, AI284509, AI582912, AI538885, AI889168, AI440263, AI866573, AI633493, AI434256, AI866469, AI434242, AI805769, AI625926, AI888661, AI500714, AI284513, AI888118, AI859991, AI436429, AI355779, AI889147, AI623736, AI581033, AI371228, AI491710, AI440252, AI431307, AI866786, AI860003, AI610557, AI431316, AI242736, AI828574, AI887499, AW151979, AI539781, AI702065, AI539707, AI885949, AI285419, AI559957, AW089557, AI521571, AI469775, AI866581, AI524654, AI567953, AI815150, AI446495, AI867068, AW074057, AI804505, AI499508, AL046466, AI963846, AW129106, AI572021, AA916133, AL045500, AI866820, AI225248, AW020397, AI890907, AI436438, AI371243, AI570056, AW075382, AW089844, AW172878, R15416, AL079799, AI284516, AI371251, AI866510, AI926593, AI866461, AI923046, AI874261, AI624293, AL047422, AI917963, AI089782, AL048403, AW151131, AA848053, AI469784, AI702073,

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20	HSKNP59	30	626946	AA480375, AI251419, AI270846, AI308612, AI270979, AA953100, AI340555, AI250202, AI309146, AW023232, AW020543, AW021400, AW021890, AI557082, AI541205, AI557697, AW022571, AW022456, AW022086, AW023469, AW021729, AW020666, AW020196, AW023029, AW022983, AI557426, AW023351, AW021816, AW022727, AW021693, AW021930, AW022981, AW021182, AW022874, AW021466, AW022593, AW023235, AW021121, AW020480, AW021059, AI541321, AW021585, AW021561, AI547225, AF040962, Y11505, S68736, Y08991, and A91160.
20	HSKNP59	62	768694	AA480375, AI251419, AI270846, AI308612, AI270979, AA953100, AI340555, AI250202, AI309146, AW023232, AW020543, AW021400, AW021890, AI557082, AI541205, AI557697, AW022571, AW022456, AW022086, AW023469, AW021729, AW020666, AW020196, AW023029, AW022983, AI557426, AW023351, AW021816, AW022727, AW021693, AW021930, AW022981, AW021182, AW022874, AW021466, AW022593, AW023235, AW021121, AW020480, AW021059, AI541321, AW021585, AW021561, AI547225, AF040962, Y11505, S68736, Y08991, and A91160.
21	HWMBB68	31	897852	AI148564, AI911259, W60958, AI683823, AW268612, AW275920, AA404358, AA443743, AI271616, AI675766, AA936391, AA403095, AI311856, AI695003, AI082141, AI079408, AA503819, AA393808, AI189388, T86418, N30670, AA393892, AA974212, AA827290, AA910984, AI014740, AA804216, AI219049, AI566294, H96780, R21152, AI374805, H23300, AI299755, R99539, N75557, R99538, AA476793,

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21	HDTGF15	64	834675	AI148564, AI911259, W60958, AI683823, AW268612, AW275920, AA404358, AI271616, AI675766, AA443743, AA936391, AA403095, AI695003, AI082141, AI311856, AA503819, T86418, N30670, AI079408, AA974212, AA393892, AA393808, AA827290, AA910984, AI014740, AI219049, AI566294, H96780, R21152, AA804216, AI189388, H23300, R99539, AI299755, N75557, R99538, AA476793, AA417638, AI374805, W05584, AI133161, AI094470, AI089034, AA905867, AA677753, T86508, AI240536, R99550, AA335337, AI538267, AA918453, AA313386, Z40615, AW445161, H92649, W87796, T33983, AW298229, R08382, H96103, H97711, R08329, H23186, H80948, T99199, N24555, AA375092, T99198, H92437, AA383378, AA419545, AF151859, AC004148, and AC009263.
21	HLWAD77	65	653513	AI148564, AI911259, W60958, AI683823, AW268612, AW275920, AA404358, AA443743, AI271616, AA936391, AI675766, AI695003, AA403095, AI311856, AI082141, AA503819, N30670, T86418, AI079408, AA393808, AA393892, AA827290, AI189388, AA910984, R21152, H96780, AI014740, AA804216, AI219049, H23300, AI566294, R99539, N75557, R99538, AI299755, AA476793, AA974212, AA417638, AI374805, AI094470, AI133161, W05584, AI089034, AA905867, T86508, AA677753, R99550, AA335337, AI240536, AA313386, AI538267, AA918453, H23186, H92649, W87796, AW445161, Z40615, T33983, AW298229, R08382, R08329, H97711, H96103, H80948, T99199, N24555, AA375092, T99198, H92437, AA383378, AA419545, AF151859, AC004148, and AC009263.
22	HWABL61	32	897731	AW328370, AW328371, AI261280, AI051959, AW044642, AI360169, AI631013, AI631025, AI091459, H18096, N53583, AA431621, AI654433, AI800320, T08343, AI399636, AI658637, AA335273, AA975921, H18136, AW005692, N54625, AA335317, H14185, AA938896, R88236, AI025281, AI439225, AI536975, AA336012, H30304, H14241, AA431334, AI090613, AI761098, AL119563, AL079734, AI085035, AI538345, AW304580, AI251034, AI887235, AI250552, AW303098, AI251284, AI251203, AA515728, AI970917,

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23	HWDQA83	66	897735	AL135118, AI083551, AA148143, AA081133, AI869871, AA143781, AW089526, H28944, AW188903, AW198015, N51465, N45114, AI873768, AA081212, AL135308, AA585237, N53605, AI433157, AI868831, AI698401, AI539153, AW089179, AW151785, AI633419, AI469532, AI866608, AI345111, AI538342, AI933785, AI955866, AI828731, AI499393, AL046926, AI802833, AI648663, AI886753, AI174394, AI365256, AI888953, AI538716, AI610645, AI886124, AW088899, AI648684, AI696819, AI539771, AI699011, AL045500, AI564719, and U67082.
25	HTPHH74	35	1155925	AI718282, AI709383, AW368622, AW272235, AW392816, AW392815, AW076072, AW392813, AI671707, AI628226, AL138202, AI887486, AI984572, AA732450, AW080807, AI859535, AI523527, AI752689, AI693382, AI984050, AW131290, AI922765, AA777248, AI832002, AI346505, AA922780, AA521201, AI954924, AA557382, AI888131, AW269811, AI608617, W72219, AI681187, AA932106, AW181955, AW392812, AA527142, AA745501, AW021226, AI889591, AW069693, AI769962, AI912432, AI419435, AI688405, AW391835, AA916772, AW168916, AI400751, N53751, AI375686, AA984515, AI690156, AI422357, AA448336, AI218693, AW392811, AI752688, AI754303, AI379872, AA988930, AW117350, AA576006, AI540975, AA196632, AA452324, AW008558, AI858111, AI300865, W44724, AA055218, AA569878, AI860850, W77963, N40921, AW130787, AI087219, AW135054, AA553499, AA156791, AI985931, AA651871, AW168405, AI700311, AW338074, AA988997, AA700296, AA621239, AI798053, AA729147, AW406945, AI351536, AA653632, AA814336, AI038164, AA570128, AI123294, AW007940, AA459461, AI914233, AL138350, AA199821, AA514830, W76103, R60314, AI168835, W72868, AA199822, AA847366, AI291058, R60370, N73108, AW026583, R18782, AA081063, AA363711, Z39606, AI798240, AA088472, AI286285, H71287, AA452102, AI061410, AA262748, AI274565, H93030, C06200, H88379, AA196914, AI434525, AA370299, AI524979, AA843973, D79669, AA621516, AW373716, T53791, AI597813, H88445, H88385, Z46043, AW021466,

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25	HTPHH74	67	899440	AI718282, AI709383, AW272235, AI887486, AI859535, AI984572, AW131290, AI523527, AI628226, AA777248, AI922765, AI346505, AA922780, AA557382, W72219, AW080807, AI608617, AA527142, AI832002, AI688405, AW391835, AA988930, AW069693, AA196632, W44724, AI300865, AA569878, AI087219, N53751, AA651871, AA553499, AI700311, AW338074, AI985931, AW168405, AW406945, AA988997, AA621239, AA700296, AI754303, AA729147, AA814336, AI351536, AA570128, AA653632, AI038164, AI123294, AI798240, AI858111, W76103, AA514830, N40921, AI168835, AW130787, AW026583, H71287, H88445, AW007940, D79669, AA847366, AI524979, W72868, T35853, W77963, AA088472, F06614, D20097, AA363711, AA081063, Z39606, D61785, H88379, H88385, AA262748, AI274565, W38656, T53791, AI798826, AW340046, D58251, H88453, AI597813, N73108, AA843973, AI096826, AW021466, AA305992, AI537191, AA747404, N56435, AA301555, D79451, AI363742, AA506127, D62111, AI889591, AA649156, AI874086, AA262641, AW392806, AA994628, C02181, AA902147, AL047100, AA370299, AI824648, AI581033, AA401830, AA291453, AA641818, AI698391, AW022636, AL037454, AL079963, AI624543, AI889189,

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26	HWABW88	36	897798	AW250365, AA447429, AW246687, AA447430, AA191517, AI292051, AW085725, AA804949, AA831450, AA582562, AI459407, H15486, H17698, AA257978, AW084939, AA457567, AA457764, AW250961, AI538335, AA642333, AA598900, AI198312, AI538216, AA312579, AA834950, AA367576, AA521042, AI248763, AI056798, AA858336, R16685, AI218663, AA682862, T83917, W87588, AA642911, F03073, W17264, AA191511, F37811, AA894565, AI375815, AA303405, AI041443, H85468, AW198159, U89387, U85510, AC006011, AC002288, AP001067, Z97053, AJ011930, AC006111, U91323, AC004841, AL096791, AP001068, and AL049835.
27	hwnfg66,HW NFG66	37	906070	AW009446, AW273128, AA524501, and AI917291.

28	HDPQG01	38	1069521	Z78342, AW275036, AI820780, AW020115, AA150284, N27708, AA016281, D80611, AA151597, AI523050, AI668603, AI185997, AI148307, N33979, AI277822, AA150386, AA458926, AI709233, AA446724, AA862368, AA946706, AA421931, W48862, AA722005, AA906072, N36527, AA045034, H16873, AA149477, AI749931, N35107, AA040052, AA861846, AA805628, N62848, W48734, AI623374, AA831459, AA446595, AW193460, AI183326, AI423718, AW296493, AI051843, AI025497, R18558, N33053, H12026, Z44707, AA609262, H00771, H25402, AA017689, H26331, R62292, Z24971, AI263557, AI123259, AI382929, H25802, H25403, H03535, AI932614, AA312980, H03451, AI803852, AW439934, C21502, H16764, N77755, R33770, AI580671, D79660, Z28673, T30082, D80610, H25761, N24537, Z40541, AA452707, R62291, N43850, D61217, AA459144, R33656, AA428166, AI017010, H11769, AA718983, N48776, R41425, AA092336, T34768, AI245435, N20866, AF077205, Z98200, and AW475060.
28	HDPQG01	69	899434	AW275036, N33979, AA446724, AA906072, AA609262, AA017689, AI123259, AI382929, AW439934, Z24971, N24537, N43850, AA459144, AA092336, T34768, N27708, T30082, H16873, AF077205, and Z98200.
28	hypad80	70	901861	AI953485, AI150769, AI271369, W56090, AA100484, F10393, AA297759, AI752351, F03251, AI752444, AA905365, AA047585, AW183209, AA447403, AI160655, N48800, R45278, AI366812, AW089943, AI918806, AA446920, AW352020, AW178617, N45592, AW178643, AI810715, AW440022, AA350505, AB029024, AB017642, AB026898, and AP000499.
28	HTXJM94	71	853413	AW275036, AA906072, AA446724, AA609262, AI123259, AI382929, AA017689, AW439934, Z24971, N24537, N33979, N43850, AA459144, T34768, N27708, T30082, H16873, AF077205, and Z98200.
29	HE2IO57	39	899432	AI675275, AA411339, AW418908, AI432460, AI417263, AI765331, AA441930, AI089276, AA446408, AA775550, R54099, AI088019, AI056121, R15968, C00373, AI400530, AI569092, AI631289, AA976916, AA748034, AW054705, AA191592, AA262484, AA843198, AW001599, AI376109, AI242622, AW105442, AI572192, AA165533, AI573163, AI338951, AI421105, AI493050, AI800245, AI051345, T35143, AI582470, AI279355, AI135735, AI381688, AI808098, W46353, AA947055, AI082835, AI378592, AA863118, AI864893, AI148300, AA525936, AA159671, AA992359, N98515, AI962766, AI952609, AI039115, AW130051, AI215162, AW338369, AI264471, AI927999,

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30	hldrr08,HLDR R08	40	906270	AF202890, AF202889, and AC007707.
31	HTOJV86	41	762837	AI685121, AI991095, AI913168, AI735017, AI302085, AI956168, AI991865, AI679903, AI620545, AI829197, AI685204, AW190397, AI833028, AI991250, AA554973, AI927762, AI459598, AW337144, AI583526, AI692817, AI963817, AI660628, AI956075, AI880450, AI818588, AI829230, AW275867, AI978631, AI814847, AI453734, AW190012, AW190228, AI625231, AI471500, AI539178, AW337938, AW192935, AW150194, AW001210, AI220226, AW273057, AI635246, AI696804, AI720447, AA402884, AI801496, AW007637, AW058222, AW338132, AI921422, AI435281, AI538691, AI735170, AI744441, AI708758, AW170593, AA402890, AW001217, AI963743, AI679773, AI539857, AI559206, AI748802, AW261992, AI829410, AI818229, AI923867, AW188532, AI923346, AW338661, AW338635, AI697171, AW189223, AI683465, AI623982, AW057732, AA610130, AI923926, AI983170, AA503365, AW131218, AI554519, AW007281, AW404803, AW190375, AI628855, AI571456, AW263007, AI804591, AA578566, AI572069, AI677647, AI565900, AI986124, AA576348, AW268534, AI811453, AI683834, AW316762, AI572084, AI624432, AI828420, AI022765, AW150841, AI446302, AW276427, AI570200, AI962904, AA573868, AI696908, AI701060, AI689647, AA523408, AI860853, AW364700, AI911650, AI587423, AW262111, AI680059, AI571990, AW194314, AI285655, AI799325, AI687917, AI151114, AA844940, AI581862, AI678689, AI570284, AI275227, AI625655, AA664201, AA523119, AI819138, AI911645, AI682577, AI749266, AA595758, AA401360, AA401336,

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31	HHBGE77	72	836039	AI741776, AI937181, AA142834, AA115742, AA449297, W07748, AI185171, AI189560, AA044208, AI127627, AA133448, AI093329, AA099349, AA040461, AI266553, W74689, N80688, AI052641, AI969190, W74787, AA043947, AA101880, AA745759, AA057190, AA678275, AI800774, T79148, AA040462, AA705309, AI277738, R05522, AI611334, AI122879, T79229, AA862428, T49145, C02622, R05630, AA046501, AA426483, AA045459, AA057125, AA035598, AI057255, AI271978, AF098269, T48600, T64288, T94106, T94194, R48539, R50308, R50595, R54836, R72044, R72788, R81845, H00997, H01634, H14534, H14621, H14914, H15754, H15902, H21803, H21804, H21946, H22030, H22241, H22276, H22339, H22340, H24583, H24760, H24805, H24952, H25060, H25142, H25143, H25234, H25437, H25439, H25447, H25481, H25484, H25552, H25575, H25581, H25597, H25667, H25723, H25873, H26093, H26123, H26170, H26171, H26188, H26253, H27449, H27498, H27570, H27706, H27707, H27758, H28405, H28468, H28675, H28682, H28687, H41899, H41904, H41938, H41943, H42228, H42347, H42482, H42486, H42825, H43015, H43016, H43117, H43612, H43672, H43724, H43726, H43905, H43988, H44045, H44288, H44317, H44407, H44445, H44541, H44599, H44656, H45249, H45272, H45437, H45458, H45465, H45524, H45552, H45794, H46631, R83358, R83490, R83794, R85978, R86022, R86091, H51902, H51910, H64505, H64518, H67527, H70718, H70719, H64505, N22028, N25275, N25316, AA235488, AA235521, AA235584, AA458497, AA464199, AA419097, AA421863, AA422158, AA428763, AA429352, AA471061, AA484184, AA484194, AA502213, AA503365, AA505465, AA507425, AA507877, AA513093, AA513282, AA522776, AA523119, AA523390, AA523408, AA534124, AA535255, AA554167, AA554973, AA581245, AA581445, AA595658, AA595758, AA610130, AA613100, AA568920, AA627124, AA639889, AA573868, AA576348, AA578566, AA578833, AA659897, AA662295, AA687945, AA740508, AA808990, AA865256, AA916021, AA916046, AA916721, AA916791, AA916874, AA931793, AA932497, AA935803, AA938643, AA948644, AA961083, AA988030, AA999945, AI000523, C02563, AA649916, AA649932, AA283741, AA290777, AA290778, AA291723, AA292541, AA400808, AA401105, and AA403266.
31	HCEFZ82	73	879185	AI672493, N21040, AW386160, AI672483, AI693512, AI138621, AA778387, AA173791,

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31	HSIED48	74	872569	AI735017, AI991095, AI833028, AI302085, AI991250, AI913168, AI459598, AI685121, AI956075, AI991865, AI880450, AI956168, AI620545, AI679903, AI539178, AW170593, AW001210, AA554973, AI927762, AI720447, AW337144, AI744441, AI685204, AI538691, AI963817, AI220226, AW190397, AI692817, AI829197, AI583526, AI735170, AI453734, AI660628, AW275867, AI748802, AI818588, AI814847, AW190012, AI978631, AW001217, AI559206, AI471500, AI923926, AW337938, AW192935, AI623982, AI696804, AI635246, AW273057, AI801496, AW007637, AW058222, AA402884, AI435281, AW338132, AI708758, AI829230, AA402890, AW150194, AI818229, AI829410, AI679773, AW261992, AW338661, AW188532, AW190228, AW338635, AW190375, AW057732, AW189223, AI923346, AI923867, AI963743, AA573868, AI539857, AA610130, AI697171, AI983170, AW131218, AI570200, AW276427, AI921422, AA503365, AI554519, AI687917, AW263007, AA578566, AI625231, AA664201, AI022765, AI986124, AW193314, AI565900, AW268534, AW404803, AI446302, AI749266, AI828420, AI696908, AW316762, AI572069, AW007281, AW150841, AI459910, AW194314, AA523408, AI680059, AI799325, AI682577, AI572084, AI571990, AI571456, AI819138, AI986014, AI624432, AA576348, AI151114, AI689647, AI860853, AI275227, AI285655, AI625655, AA844940, AI581862, AA523119, AI572628, AI683834, AI804591, AA578833, AI991849, AI587047, AI570284, AI628855, AI673632, AI811754, AW401348, AW001504, AA581445, AI275814, AA429352, AW084943, AW364700, AI587186, AI598095, AI281742, AA523390, AA568920, AI984847, AI678689, AI573201, AI983804, AI911650, AI697003, AI683481, AI984126, AA595758, AI829224, AI587423, AI983983, AI571646, AI677647, AI660451, AA522776, AI922800, AI696995, AI673816, AI559261, AI660213, AA845885, AI686934, AI521342, AI570045, AI955753, AI567553, AI697246, AI125317, AI624660, AI986042, AI962904, AW191013, AW193403, AI627913, AI690842, AI598025, AI701060, AI624165, AI597973, AI632055, AI439833, AW085666, AI991212, AW264686, AW405737, AI566478, AI570063, AI805478, AA659897, AI564660, AI811453, AI453141, AI566489, AI677995, AI858139, AI587494, AI750165, AI635785, AI610183, AI460298, AI961478, AA464199, AI631417, AI813866, AW050723, AI963186, AI708951, AI865827,

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31	hadfw77	75	847205	AI741776, AI937181, AA142834, AA449297, AA115742, W07748, AI185171, AI189560, AA044208, AI127627, AA133448, AI093329, AA099349, AI266553, AA040461, W74689, N80688, AI052641, AI969190, AA745759, AA043947, AA101880, W74787, AA057190, AA678275, AI800774, T79148, AA040462, AA705309, AI277738, T49144, R05522, AI611334, AI122879, D78874, AA862428, T79229, T49145, C02622, R05630, AA046501, AA449557, AA426483, AA045459, AA057125, AA035598, AI057255, AI271978, and AF098269.
31	HNGFW58	76	833074	AL044254, AA641592, AL044209, AL135706, AI800268, AA584638, AW238615, AA533107, AA489896, AI936549, AL043065, AA714323, AI554666, AA577860, AA584801, AI922061, AA569180, AI868368, AA121904, AI052560, AI349954, AA501775, AA664366, AA553442, AA258511, AI061445, AW270592, AA333509, AA778649, AA487808, AA481809, AA679179, AA736957, AA640504, AA612822, AA657354, AA227298, AI401729, AI821285, H80568, AA766720, D59168, AA280232, AA769976, AW075927, AA084302, AA055576, AI923902, T63143, AA602337, AA720668, AA376315, AA551539, C16656, AI033961, T07820, AI525330, AA744577, T66926, AL134095, D56198, AA377887, AA780457, AA744267, AA745439, AA744408, T02931, AA883167, AA283645, N57818, F25744, AW028252, AF088219, AL136520, AC007344, AC003658, AP000034, AP000101, AP000264, AC005386, AC006364, AC007317, U66059, AC002449, AL049710, AL031286, AL049743, AC002070, AL049834, AL023875, AC006203, AC005019, AL110505, AC000119, AC002080, AL109628, AL132994, AC007402, AP000460, AL133162, U69730, AL034400, AC004823, AL049734, AC004677, AC004470, AC004894, AC003686, AC004072, AC005588, AC004949, Z68326, Z80774, AC008394, AC006249, AC004158, AL021068, AC002463, Z68280, L11910, AC007632, AL035671, AC002454, AC004908, AL133500, AC004842, AL049565, AL132777, AC004852, AC005794, AC004544, AC007065, AC007690, AL030996, AC003986, AC006336, AC003081, AL031274, AP000566, AC005739, AC007253, AC005034, AL035695, AC005823, AC005686, AP000692, Z84720, AC007319, U40455, AL022345, AL035699, AC007748, AC000378, AC007446, AP000457, AC005859, AL009176, Z82899, Z84470, AL031114, AL049838, AC005273, AL049641, AC006204, AC006461, L29074, AL033521, AC004774, AL034377, AC005064, AL023495, Z96074, AF101874, U01882, AC004454, AC005230, Z68871, AC005050, AL035688, AJ225782,

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				X72818, X79834, L03174, E12557, A68511, and X72819.
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Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

5

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector.

10 Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being

15 isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited</u>
	<u>Plasmid</u>	
	Lambda Zap	pBluescript (pBS)
20	Uni-Zap XR	pBluescript (pBS)
	Zap Express	pBK
	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSPORT 2.0	pCMVSPORT 2.0
25	pCMVSPORT 3.0	pCMVSPORT 3.0
	pCR [®] 2.1	pCR [®] 2.1

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res.

30 16:7583-7600 (1988); Altting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Altting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey

Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

10 Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

25 The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample 30 may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

- 5 Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P - γ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).)
- 10 The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate.
- 15 These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

- Alternatively, two primers of 17-20 nucleotides derived from both ends of the
- 20 SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 μg of the above cDNA template. A convenient reaction mixture is
- 25 1.5-5 mM MgCl_2 , 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and
- 30 the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue Distribution of Polypeptide

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P³² using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70 degree C overnight, and the films developed according to standard procedures.

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95 degree C; 1 minute, 56 degree C; 1 minute, 70 degree C. This cycle is repeated 32 times followed by one 5 minute cycle at 70 degree C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as
5 BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a
10 ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain
15 M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

20 Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.⁶⁰⁰) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1
25 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4 degree C. The cell debris
30 is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with

high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then
5 washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-
10 NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50
15 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4 degree C or frozen at -80 degree C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC
20 Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The
25 promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR
30 primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

5 The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10 degree C.

 Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10 degree C and the cells harvested by continuous
10 centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

15 The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

20 The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4 degree C overnight to allow further GuHCl extraction.

 Following high speed centrifugation (30,000 xg) to remove insoluble particles,
25 the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4 degree C without mixing for 12 hours prior to further purification steps.

 To clarify the refolded polypeptide solution, a previously prepared tangential
30 filtration unit equipped with 0.16 um membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive

Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

5 Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40
10 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

15 The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 ug of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL
20 assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus

Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a
25 polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the
30 plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral

sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five ug of a plasmid containing the polynucleotide is co-transfected with 1.0 ug of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One ug
5 of BaculoGold™ virus DNA and 5 ug of the plasmid are mixed in a sterile well of a microtiter plate containing 50 ul of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 ul Lipofectin plus 90 ul Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded
10 in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27 degrees C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27 degrees C for four days.

After four days the supernatant is collected and a plaque assay is performed,
15 as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page
20 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 ul of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are
25 harvested and then they are stored at 4 degree C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the
30 medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 uCi of ³⁵S-methionine and 5 uCi ³⁵S-cysteine (available from Amersham) are added.

The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of
5 purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which
10 mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long
15 terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden),
20 pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

25 Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the
30 encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of

interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279
5 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

10 Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g.,
15 with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate
20 restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide.
25 Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1%
30 agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector

are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for
5 transfection. Five μ g of the expression plasmid pC6 a pC4 is cotransfected with 0.5
ug of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-
neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an
enzyme that confers resistance to a group of antibiotics including G418. The cells are
seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the
10 cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in
alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1
mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in
6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50
nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest
15 concentrations of methotrexate are then transferred to new 6-well plates containing
even higher concentrations of methotrexate (1 μ M, 2 μ M, 5 μ M, 10 mM, 20 mM).
The same procedure is repeated until clones are obtained which grow at a
concentration of 100 - 200 μ M. Expression of the desired gene product is analyzed,
for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

20

Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other
proteins. These fusion proteins can be used for a variety of applications. For
example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG
25 domains, and maltose binding protein facilitates purification. (See Example 5; see
also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to
IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization
signals fused to the polypeptides of the present invention can target the protein to a
specific subcellular localization, while covalent heterodimer or homodimers can
30 increase or decrease the activity of a fusion protein. Fusion proteins can also create
chimeric molecules having more than one function. Finally, fusion proteins can
increase solubility and/or stability of the fused protein compared to the non-fused

protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

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GGGATCCGGAGCCCAAATCTTCTGACAAAACACACATGCCACCGTG  
CCAGCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAAA  
CCCAAGGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGT  
GGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGG  
ACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTA  
CAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACT  
GGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCA  
ACCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAAC  
CACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAG  
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGT  
GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGACCACGCCT  
CCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTG
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GACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCA
TGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

5 **Example 10: Production of an Antibody from a Polypeptide**

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred
10 method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal
15 antibodies can be prepared using hybridoma technology. (Köhler et al., Nature 256:495 (1975); Köhler et al., Eur. J. Immunol. 6:511 (1976); Köhler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more
20 preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56 degrees C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 ug/ml of streptomycin.

25 The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as
30 described by Wands et al. (Gastroenterology 80:225-232 (1981).) The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')₂ and other fragments of the antibodies of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

Example 11: Production Of Secreted Protein For High-Throughput Screening

Assays

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described herein.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2×10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degrees C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl₂ (anhyd); 0.00130

mg/L $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$; 0.050 mg/L of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$; 0.417 mg/L of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$; 311.80 mg/L of KCl; 28.64 mg/L of MgCl_2 ; 48.84 mg/L of MgSO_4 ; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO_3 ; 62.50 mg/L of $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$; 71.02 mg/L of Na_2HPO_4 ; .4320 mg/L of $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine- H_2O ; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL- H_2O ; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL- H_2O ; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2 H_2O ; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B₁₂; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person

B adds 1.5ml appropriate media to each well. Incubate at 37 degrees C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants
5 from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the
10 invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 12: Construction of GAS Reporter Construct

One signal transduction pathway involved in the differentiation and
15 proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors
20 called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at
25 higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2,
30 Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, *Ann. Rev. Biochem.* 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN- α , IFN- γ , and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

<u>Ligand</u>	<u>tyk2</u>	<u>JAKs</u>		<u>Jak3</u>	<u>STATS</u>	<u>GAS(elements) or ISRE</u>
		<u>Jak1</u>	<u>Jak2</u>			
<u>IFN family</u>						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
Il-10	+	?	?	-	1,3	
<u>gp130 family</u>						
IL-6 (Pleiotrophic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
Il-11(Pleiotrophic)	?	+	?	?	1,3	
OnM(Pleiotrophic)	?	+	+	?	1,3	
LIF(Pleiotrophic)	?	+	+	?	1,3	
CNTF(Pleiotrophic)	-/+	+	+	?	1,3	
G-CSF(Pleiotrophic)	?	+	?	?	1,3	
IL-12(Pleiotrophic)	+	-	+	+	1,3	
<u>g-C family</u>						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
<u>gp140 family</u>						
IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS
<u>Growth hormone family</u>						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
<u>Receptor Tyrosine Kinases</u>						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	
CSF-1	?	+	+	-	1,3	GAS (not IRF1)

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCGAAATGATTTCCTCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTGGCAAAGCCTAGGC:3' (SEQ ID NO:4)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCAGAGATTTCCTCCGAAATCTAGATTTCCTCCGAAATGATTTCCTCCGAAATGATTTCCTCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCTAACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGGCAAAGCTT:3' (SEQ ID NO:5)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not
5 contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using Sall and NotI, and inserted into a backbone vector containing the neomycin resistance
10 gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS
15 with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-
20 2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 13: High-Throughput Screening Assay for T-cell Activity.

25 The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway.
30 The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1% Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1×10^7 cells in OPTI-MEM to T25 flask and incubate at 37 degrees C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptides of the invention and/or induced polypeptides of the invention as produced by the protocol described in Example 11.

On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degrees C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4 degrees C and serve as a source of material for repeating the assay on a specific well if desired.

As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

Example 14: High-Throughput Screening Assay Identifying Myeloid Activity

The following protocol is used to assess myeloid activity by determining whether polypeptides of the invention proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest 2×10^7 U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM Na₂HPO₄·7H₂O, 1 mM MgCl₂, and 675 uM CaCl₂. Incubate at 37 degrees C for 45 min.

- 5 Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degrees C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

- 10 These cells are tested by harvesting 1×10^8 cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of 5×10^5 cells/ml. Plate 200 ul cells per well in the 96-well plate (or 1×10^5 cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example

- 15 11. Incubate at 37 degrees C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

20 **Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.**

- When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the
- 25 EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat pheochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor).

- 30 The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

- 5 5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:6)
 5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the
10 EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and
15 allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is
20 done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine
25 growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640
30 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count

the cell number and add more low serum medium to reach final cell density as 5×10^5 cells/ml.

Add 200 μ l of the cell suspension to each well of 96-well plate (equivalent to 1×10^5 cells/well). Add 50 μ l supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ μ l of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

10 **Example 16: High-Throughput Screening Assay for T-cell Activity**

NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF-KB would be useful in treating diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTCCCC) (SEQ ID NO:8), 18 bp of sequence

complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)

- 5 The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)

- PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is
10 digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)
Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

- 5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCC
15 ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC
ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGA
CTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTA
TTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA
GCTT:3' (SEQ ID NO:10)

20

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

- 25 In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

- 30 Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described

in Example 13. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 17: Assay for SEAP Activity

5 As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

10 Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room
15 temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

20 Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5

25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO₂ incubator for

20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO₂ incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to $2-5 \times 10^6$ cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1×10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4. The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca⁺⁺ concentration.

Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is

unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in

Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na₃VO₄, 2 mM Na₄P₂O₇ and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is
5 shaken on a rotating shaker for 5 minutes at 4 degrees C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after
10 detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degrees C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

15 Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for
20 a range of tyrosine kinases and are available from Boehringer Mannheim.

The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg₂⁺ (5mM ATP/50mM MgCl₂), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl₂, 5 mM MnCl₂,
25 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degrees C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

30 Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degrees C for 20

min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degrees C for
5 one hour. Wash the well as above.

Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of
10 tyrosine kinase activity.

Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity

As a potential alternative and/or compliment to the assay of protein tyrosine
15 kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase,
20 Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are
25 then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at
30 4 degrees C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and

cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

5 After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard
10 procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

15 **Example 21: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide**

 RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA
20 is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

 PCR products are then sequenced using primers labeled at their 5' end with T4
25 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

30 PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United

States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenin deoxy-uridine 5'-triphosphate (Boehringer Mannheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in

Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 23: Formulation

The invention also provides methods of treatment and/or prevention diseases, disorders, and/or conditions (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant a polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

Therapeutics can be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials

(for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al.,
5 Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

Sustained-release Therapeutics also include liposomally entrapped
10 Therapeutics of the invention (*see generally*, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang
15 et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the
20 optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

25 Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically
30 acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation.

For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both.

5 Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

10 The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten
15 residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA; sugar
20 alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or
25 stabilizers will result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a
30 stopper pierceable by a hypodermic injection needle.

Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized

formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

5 The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use
10 or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

 The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus
15 deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to,
20 Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B,
25 whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic
30 mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate

administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not
5 limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are
10 administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

15 In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta),
20 OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), TR6 (International Publication No. WO 98/30694), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF),
25 and soluble forms of Fas, CD30, CD27, CD40 and 4-1BB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International
30 Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICLOVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In

another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment,

5 Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat
10 or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with
15 ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment,
20 Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered
25 with the Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin,
30 beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin,

erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

Conventional nonspecific immunosuppressive agents, that may be
5 administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

In specific embodiments, Therapeutics of the invention are administered in
10 combination with immunosuppressants. Immunosuppressants preparations that may be administered with the Therapeutics of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucocorticosteroids, and RAPAMUNE™ (sirolimus). In a specific
15 embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the
20 Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

25 In an additional embodiment, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives,
30 pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-

acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

5 In another embodiment, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-
10 FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl
15 estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephallen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and
20 etoposide).

 In a specific embodiment, Therapeutics of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, Therapeutics of the invention are administered in combination with
25 Rituximab. In a further embodiment, Therapeutics of the invention are administered with Rituxmab and CHOP, or Rituxmab and any combination of the components of CHOP.

 In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered
30 with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered

with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are incorporated herein by reference herein.

In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but

are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example,
5 radiation therapy.

Example 24: Method of Treating Decreased Levels of the Polypeptide

The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising
10 administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the
15 secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily
20 dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

Example 25: Method of Treating Increased Levels of the Polypeptide

25 The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

30 In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of

decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer. For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

Example 26: Method of Treatment Using Gene Therapy-Ex Vivo

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is

maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

5 The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the
10 packaging cells are now referred to as producer cells).

 Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is
15 removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been
20 efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

 The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

25 **Example 27: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention**

 Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent
30 NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935

(1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining
5 cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na₂ HPO₄, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains
10 approximately 3×10^6 cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with
15 HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3'end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3'end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5'end and a HindIII site at the 3'end. The CMV promoter and the
20 fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap
25 (Bio-Rad). The final DNA concentration is generally at least 120 µg/ml. 0.5 ml of the cell suspension (containing approximately 1.5×10^6 cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 µF and 250-300 V, respectively. As voltage increases, cell survival decreases, but
30 the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following
5 day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a
10 patient as described above.

Example 28: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the
15 introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in
20 the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

25 The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

30 The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or

precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations. (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg

body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence
5 can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or
10 mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard
15 recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on
20 the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

25 After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 μ m cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA
30 in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper

dosages and other treatment parameters in humans and other animals using naked DNA.

Example 29: Transgenic Animals.

5 The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are
10 used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

 Any technique known in the art may be used to introduce the transgene (*i.e.*, polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear
15 microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic
20 stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, *e.g.*, Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-
25 mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

 Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into
30 enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or
5 head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When
10 it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the
15 nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent
20 to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA
25 expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies
30 specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding

strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of
5 heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of
10 interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying diseases, disorders, and/or conditions associated with aberrant expression, and in screening for compounds effective in
15 ameliorating such diseases, disorders, and/or conditions.

Example 30: Knock-Out Animals.

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*,
20 see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding
25 regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination,
30 results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas &

Capeocchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

5 In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not
10 limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention,
15 e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve
20 expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

 Alternatively, the cells can be incorporated into a matrix and implanted in the
25 body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

30 When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For

example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying diseases, disorders, and/or conditions associated with aberrant expression, and in screening for compounds effective in ameliorating such diseases, disorders, and/or conditions.

10 **Example 31: Production of an Antibody**

a) Hybridoma Technology

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide(s) of the invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide(s) of the invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide(s) of the invention are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide(s) of the invention, or, more preferably, with a secreted polypeptide-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line

(SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which
5 secrete antibodies capable of binding the polypeptide(s) of the invention.

Alternatively, additional antibodies capable of binding polypeptide(s) of the invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In
10 accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide(s) of the invention protein-specific antibody can be blocked by polypeptide(s) of the invention.
15 Such antibodies comprise anti-idiotypic antibodies to the polypeptide(s) of the invention protein-specific antibody and are used to immunize an animal to induce formation of further polypeptide(s) of the invention protein-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells
20 producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO
25 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

b) Isolation Of Antibody Fragments Directed

polypeptide(s) of the invention From A Library Of scFvs

30 Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide(s) of the

invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

Rescue of the Library. A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 10⁹ E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 10⁸ TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 µg/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37°C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 µm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10¹³ transducing units/ml (ampicillin-resistant clones).

Panning of the Library. Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 µg/ml or 10 µg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 10¹³ TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to

stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 µg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 32: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation

Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can,

in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective
5 ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the
10 detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

In Vitro Assay- Purified polypeptides of the invention, or truncated forms thereof, is assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the
15 polypeptides of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as
20 IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

25 Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added 10^5 B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5×10^{-5} M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and 10^{-5} dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with 3 H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The
30 positive and negative controls are IL2 and medium respectively.

In Vivo Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of a polypeptide of the invention, or truncated forms thereof. Mice

receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with polypeptides of the invention identify the results of the activity of the polypeptides on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with polypeptide is used to indicate whether the polypeptide specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and polypeptide-treated mice.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides of the invention (e.g., gene therapy), agonists, and/or antagonists of polynucleotides or polypeptides of the invention.

Example 33: T Cell Proliferation Assay

Proliferation assay for Resting PBLs.

A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ^3H -thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 microliters per well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 °C (1 microgram/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5×10^4 /well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of TNF Delta and/or TNF Epsilon protein (total volume 200 microliters). Relevant protein buffer and medium alone are controls.

After 48 hr. culture at 37 °C, plates are spun for 2 min. at 1000 rpm and 100 microliters of supernatant is removed and stored -20 °C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 microliters of medium containing 0.5 microcuries of ³H-thymidine and cultured at 37 °C for 18-24 hr. Wells are harvested and incorporation of ³H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of TNF Delta and/or TNF Epsilon proteins.

Alternatively, a proliferation assay on resting PBL (peripheral blood lymphocytes) is measured by the up-take of ³H-thymidine. The assay is performed as follows. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% (Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non-adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using 2 x 10⁴ cells/well in a final volume of 200 microliters. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60ul are added to 140ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector (negative control), IL-2 (*), IFN γ , TNF α , IL-10 and TR2. In addition to the control supernatants, recombinant human IL-2 (R & D Systems, Minneapolis, MN) at a final concentration of 100ng/ml is also used. After 24 hours of culture, each well is pulsed with 1uCi of ³H-thymidine (Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of ³H-thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

(*) The amount of the control cytokines IL-2, IFN γ , TNF α and IL-10 produced in each transfection varies between 300pg to 5ng/ml.

Costimulation assay.

A costimulation assay on resting PBL (peripheral blood lymphocytes) is performed in the presence of immobilized antibodies to CD3 and CD28. The use of antibodies specific for the invariant regions of CD3 mimic the induction of T cell activation that would occur through stimulation of the T cell receptor by an antigen. Cross-linking of the TCR (first signal) in the absence of a costimulatory signal (second signal) causes very low induction of proliferation and will eventually result in a state of "anergy", which is characterized by the absence of growth and inability to produce cytokines. The addition of a costimulatory signal such as an antibody to CD28, which mimics the action of the costimulatory molecule. B7-1 expressed on activated APCs, results in enhancement of T cell responses including cell survival and production of IL-2. Therefore this type of assay allows to detect both positive and negative effects caused by addition of supernatants expressing the proteins of interest on T cell proliferation.

The assay is performed as follows. Ninety-six well plates are coated with 100ng/ml anti-CD3 and 5ug/ml anti-CD28 (Pharmingen, San Diego, CA) in a final volume of 100ul and incubated overnight at 4C. Plates are washed twice with PBS before use. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using 2×10^4 cells/well in a final volume of 200ul. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60ul are added to 140ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector only (negative control), IL-2, IFN γ , TNF α , IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 (R & D Systems, Minneapolis, MN) at a final concentration of 10ng/ml is also used. After 24 hours of culture, each well is

pulsed with 1uCi of ^3H -thymidine (Nen, Boston, MA). Cells are then harvested 20 hours following pulsing and incorporation of ^3H -thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

5 Costimulation assay: IFN γ and IL-2 ELISA

The assay is performed as follows. Twenty-four well plates are coated with either 300ng/ml or 600ng/ml anti-CD3 and 5ug/ml anti-CD28 (Pharmingen, San Diego, CA) in a final volume of 500ul and incubated overnight at 4C. Plates are washed twice with PBS before use. PBMC are isolated by Ficoll (LSM, ICN Biotechnologies, Aurora, Ohio) gradient centrifugation from human peripheral blood, and are cultured overnight in 10% FCS(Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD). This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non adherent cells are collected, washed and used in the costimulation assay. The assay is performed in the pre-coated twenty-four well plate using 1×10^5 cells/well in a final volume of 900ul. The supernatants (293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 300ul are added to 600ul of 10% FCS/RPMI containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector only(negative control), IL-2, IFN γ , IL-12 and IL-18. In addition to the control supernatants recombinant human IL-2 (all cytokines were purchased from R & D Systems, Minneapolis, MN) at a final concentration of 10ng/ml, IL-12 at a final concentration of 1ng/ml and IL-18 at a final concentration of 50ng/ml are also used. Controls and unknown samples are tested in duplicate. Supernatant samples (250ul) are collected 2 days and 5 days after the beginning of the assay. ELISAs to test for IFN γ and IL-2 secretion are performed using kits purchased from R & D Systems, (Minneapolis, MN). Results are expressed as an average of duplicate samples plus or minus standard error.

30

Proliferation assay for preactivated-resting T cells.

A proliferation assay on preactivated-resting T cells is performed on cells that are previously activated with the lectin phytohemagglutinin (PHA). Lectins are polymeric plant proteins that can bind to residues on T cell surface glycoproteins including the TCR and act as polyclonal activators. PBLs treated with PHA and then
5 cultured in the presence of low doses of IL-2 resemble effector T cells. These cells are generally more sensitive to further activation induced by growth factors such as IL-2. This is due to the expression of high affinity IL-2 receptors that allows this population to respond to amounts of IL-2 that are 100 fold lower than what would have an effect on a naïve T cell. Therefore the use of this type of cells might enable
10 to detect the effect of very low doses of an unknown growth factor, that would not be sufficient to induce proliferation on resting (naïve) T cells.

The assay is performed as follows. PBMC are isolated by F/H gradient centrifugation from human peripheral blood, and are cultured in 10% FCS (Fetal Calf Serum, Biofluids, Rockville, MD)/RPMI (Gibco BRL, Gaithersburg, MD) in the
15 presence of 2 µg/ml PHA (Sigma, Saint Louis, MO) for three days. The cells are then washed in PBS and cultured in 10% FCS/RPMI in the presence of 5 ng/ml of human recombinant IL-2 (R & D Systems, Minneapolis, MN) for 3 days. The cells are washed and rested in starvation medium (1% FCS/RPMI) for 16 hours prior to the beginning of the proliferation assay. An aliquot of the cells is analyzed by FACS to
20 determine the percentage of T cells (CD3 positive cells) present; this usually ranges between 93-97% depending on the donor. The assay is performed in a 96 well plate using 2×10^4 cells/well in a final volume of 200 µl. The supernatants (e.g., CHO or 293T supernatants) expressing the protein of interest are tested at a 30% final dilution, therefore 60 µl are added to 140 µl of 10% FCS/RPMI containing the cells. Control
25 supernatants are used at the same final dilution and express the following proteins: vector (negative control), IL-2, IFN γ , TNF α , IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 at a final concentration of 10 ng/ml is also used. After 24 hours of culture, each well is pulsed with 1 µCi of ^3H -thymidine (Nen, Boston, MA). Cells are then harvested 20 hours following pulsing
30 and incorporation of ^3H -thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

The studies described in this example test activity of polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides of the invention (e.g., gene therapy), agonists, and/or antagonists of polynucleotides or polypeptides of the invention.

5

Example 34: Effect of Polypeptides of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells

10 Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF- α , causes a rapid
15 change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC γ RII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

FACS analysis of surface antigens is performed as follows. Cells are treated 1-3
20 days with increasing concentrations of polypeptides of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

25

Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Th1 helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to
30 measure the IL-12 release as follows. Dendritic cells (10^6 /ml) are treated with increasing concentrations of polypeptides of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell

cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

- 5 Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the
10 antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

- FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of polypeptides of the invention or
15 LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

- 20 Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Polypeptides, agonists, or antagonists of the invention can be
25 screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

30

Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results

from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of 2×10^6 /ml in PBS containing PI at a final concentration of 5 µg/ml, and then incubated at room temperature for 5 minutes before FACSscan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of 5×10^5 cells/ml with increasing concentrations of the a polypeptide of the invention and under the same conditions, but in the absence of the polypeptide. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of a polypeptide of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e.g., R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

Oxidative burst. Purified monocytes are plated in 96-w plate at 2×10^5 cell/well. Increasing concentrations of polypeptides of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 µl 1N NaOH per well. The absorbance is read at 610

nm. To calculate the amount of H₂O₂ produced by the macrophages, a standard curve of a H₂O₂ solution of known molarity is performed for each experiment.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polypeptides, polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 35: Biological Effects of Polypeptides of the Invention

Astrocyte and Neuronal Assays

Recombinant polypeptides of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate a polypeptide of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA* 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of a polypeptide of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

Fibroblast and endothelial cell assays

Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE₂ assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or polypeptides of the invention with or without IL-1 α for 24 hours. The supernatants are collected and assayed for PGE₂ by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without polypeptides of the invention IL-1 α for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or polypeptides of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with polypeptides of the invention.

Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP⁺) and released.

Subsequently, MPP⁺ is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP⁺ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotinamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

Based on the data with FGF-2, polypeptides of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of a polypeptide of the invention is first examined *in vitro* in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm² on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days *in vitro* and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if a polypeptide of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the polypeptide may be involved in Parkinson's Disease.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

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Example 36: The Effect of Polypeptides of the Invention on the Growth of Vascular Endothelial Cells

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at $2-5 \times 10^4$ cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnology, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. A polypeptide having the amino acid sequence of SEQ ID NO:Y, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

An increase in the number of HUVEC cells indicates that the polypeptide of the invention may proliferate vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 37: Stimulatory Effect of Polypeptides of the Invention on the Proliferation of Vascular Endothelial Cells

For evaluation of mitogenic activity of growth factors, the colorimetric MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)2H-tetrazolium) assay with the electron coupling reagent PMS (phenazine methosulfate) was performed (CellTiter 96 AQ, Promega). Cells are seeded in a 96-well plate (5,000 cells/well) in 0.1 mL serum-supplemented medium and are allowed to attach overnight. After serum-starvation for 12 hours in 0.5% FBS, conditions (bFGF, VEGF₁₆₅ or a

polypeptide of the invention in 0.5% FBS) with or without Heparin (8 U/ml) are added to wells for 48 hours. 20 mg of MTS/PMS mixture (1:0.05) are added per well and allowed to incubate for 1 hour at 37°C before measuring the absorbance at 490 nm in an ELISA plate reader. Background absorbance from control wells (some media, no cells) is subtracted, and seven wells are performed in parallel for each condition. See, Leak *et al.* *In Vitro Cell. Dev. Biol.* 30A:512-518 (1994).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 38: Inhibition of PDGF-induced Vascular Smooth Muscle Cell Proliferation Stimulatory Effect

HAoSMC proliferation can be measured, for example, by BrdUrd incorporation. Briefly, subconfluent, quiescent cells grown on the 4-chamber slides are transfected with CRP or FITC-labeled AT2-3LP. Then, the cells are pulsed with 10% calf serum and 6 mg/ml BrdUrd. After 24 h, immunocytochemistry is performed by using BrdUrd Staining Kit (Zymed Laboratories). In brief, the cells are incubated with the biotinylated mouse anti-BrdUrd antibody at 4 degrees C for 2 h after being exposed to denaturing solution and then incubated with the streptavidin-peroxidase and diaminobenzidine. After counterstaining with hematoxylin, the cells are mounted for microscopic examination, and the BrdUrd-positive cells are counted. The BrdUrd index is calculated as a percent of the BrdUrd-positive cells to the total cell number. In addition, the simultaneous detection of the BrdUrd staining (nucleus) and the FITC uptake (cytoplasm) is performed for individual cells by the concomitant use of bright field illumination and dark field-UV fluorescent illumination. See, Hayashida et al., *J. Biol. Chem.* 6:271(36):21985-21992 (1996).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 39: Stimulation of Endothelial Migration

This example will be used to explore the possibility that a polypeptide of the invention may stimulate lymphatic endothelial cell migration.

Endothelial cell migration assays are performed using a 48 well microchemotaxis chamber (Neuroprobe Inc., Cabin John, MD; Falk, W., et al., J. Immunological Methods 1980;33:239-247). Polyvinylpyrrolidone-free polycarbonate filters with a pore size of 8 μ m (Nucleopore Corp. Cambridge, MA) are coated with 0.1% gelatin for at least 6 hours at room temperature and dried under sterile air. Test substances are diluted to appropriate concentrations in M199 supplemented with 0.25% bovine serum albumin (BSA), and 25 μ l of the final dilution is placed in the lower chamber of the modified Boyden apparatus. Subconfluent, early passage (2-6) HUVEC or BMEC cultures are washed and trypsinized for the minimum time required to achieve cell detachment. After placing the filter between lower and upper chamber, 2.5×10^5 cells suspended in 50 μ l M199 containing 1% FBS are seeded in the upper compartment. The apparatus is then incubated for 5 hours at 37°C in a humidified chamber with 5% CO₂ to allow cell migration. After the incubation period, the filter is removed and the upper side of the filter with the non-migrated cells is scraped with a rubber policeman. The filters are fixed with methanol and stained with a Giemsa solution (Diff-Quick, Baxter, McGraw Park, IL). Migration is quantified by counting cells of three random high-power fields (40x) in each well, and all groups are performed in quadruplicate.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

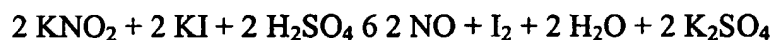
Example 40: Stimulation of Nitric Oxide Production by Endothelial Cells

Nitric oxide released by the vascular endothelium is believed to be a mediator of vascular endothelium relaxation. Thus, activity of a polypeptide of the invention can be

assayed by determining nitric oxide production by endothelial cells in response to the polypeptide.

Nitric oxide is measured in 96-well plates of confluent microvascular endothelial cells after 24 hours starvation and a subsequent 4 hr exposure to various levels of a positive control (such as VEGF-1) and the polypeptide of the invention. Nitric oxide in the medium is determined by use of the Griess reagent to measure total nitrite after reduction of nitric oxide-derived nitrate by nitrate reductase. The effect of the polypeptide of the invention on nitric oxide release is examined on HUVEC.

Briefly, NO release from cultured HUVEC monolayer is measured with a NO-specific polarographic electrode connected to a NO meter (Iso-NO, World Precision Instruments Inc.) (1049). Calibration of the NO elements is performed according to the following equation:



The standard calibration curve is obtained by adding graded concentrations of KNO₂ (0, 5, 10, 25, 50, 100, 250, and 500 nmol/L) into the calibration solution containing KI and H₂SO₄. The specificity of the Iso-NO electrode to NO is previously determined by measurement of NO from authentic NO gas (1050). The culture medium is removed and HUVECs are washed twice with Dulbecco's phosphate buffered saline. The cells are then bathed in 5 ml of filtered Krebs-Henseleit solution in 6-well plates, and the cell plates are kept on a slide warmer (Lab Line Instruments Inc.) To maintain the temperature at 37°C. The NO sensor probe is inserted vertically into the wells, keeping the tip of the electrode 2 mm under the surface of the solution, before addition of the different conditions. S-nitroso acetyl penicillamin (SNAP) is used as a positive control. The amount of released NO is expressed as picomoles per 1x10⁶ endothelial cells. All values reported are means of four to six measurements in each group (number of cell culture wells). See, Leak *et al. Biochem. and Biophys. Res. Comm.* 217:96-105 (1995).

The studies described in this example tested activity of polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 41: Effect of Polypeptides of the Invention on Cord Formation in Angiogenesis

Another step in angiogenesis is cord formation, marked by differentiation of endothelial cells. This bioassay measures the ability of microvascular endothelial cells to form capillary-like structures (hollow structures) when cultured *in vitro*.

CADMEC (microvascular endothelial cells) are purchased from Cell Applications, Inc. as proliferating (passage 2) cells and are cultured in Cell Applications' CADMEC Growth Medium and used at passage 5. For the *in vitro* angiogenesis assay, the wells of a 48-well cell culture plate are coated with Cell Applications' Attachment Factor Medium (200 ml/well) for 30 min. at 37°C. CADMEC are seeded onto the coated wells at 7,500 cells/well and cultured overnight in Growth Medium. The Growth Medium is then replaced with 300 mg Cell Applications' Chord Formation Medium containing control buffer or a polypeptide of the invention (0.1 to 100 ng/ml) and the cells are cultured for an additional 48 hr. The numbers and lengths of the capillary-like chords are quantitated through use of the Boeckeler VIA-170 video image analyzer. All assays are done in triplicate.

Commercial (R&D) VEGF (50 ng/ml) is used as a positive control. b-esteradiol (1 ng/ml) is used as a negative control. The appropriate buffer (without protein) is also utilized as a control.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 42: Angiogenic Effect on Chick Chorioallantoic Membrane

Chick chorioallantoic membrane (CAM) is a well-established system to examine angiogenesis. Blood vessel formation on CAM is easily visible and quantifiable. The ability of polypeptides of the invention to stimulate angiogenesis in CAM can be examined.

Fertilized eggs of the White Leghorn chick (*Gallus gallus*) and the Japanese quail (*Coturnix coturnix*) are incubated at 37.8°C and 80% humidity. Differentiated CAM of 16-day-old chick and 13-day-old quail embryos is studied with the following methods.

On Day 4 of development, a window is made into the egg shell of chick eggs. The embryos are checked for normal development and the eggs sealed with cellotape. They are further incubated until Day 13. Thermanox coverslips (Nunc, Naperville, IL) are cut into disks of about 5 mm in diameter. Sterile and salt-free growth factors are dissolved in distilled water and about 3.3 mg/ 5 ml are pipetted on the disks. After air-drying, the inverted disks are applied on CAM. After 3 days, the specimens are fixed in 3% glutaraldehyde and 2% formaldehyde and rinsed in 0.12 M sodium cacodylate buffer. They are photographed with a stereo microscope [Wild M8] and embedded for semi- and ultrathin sectioning as described above. Controls are performed with carrier disks alone.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 43: Angiogenesis Assay Using a Matrigel Implant in Mouse

In vivo angiogenesis assay of a polypeptide of the invention measures the ability of an existing capillary network to form new vessels in an implanted capsule of murine extracellular matrix material (Matrigel). The protein is mixed with the liquid Matrigel at 4 degree C and the mixture is then injected subcutaneously in mice where it solidifies. After 7 days, the solid "plug" of Matrigel is removed and examined for the presence of new blood vessels. Matrigel is purchased from Becton Dickinson Labware/Collaborative Biomedical Products.

When thawed at 4 degree C the Matrigel material is a liquid. The Matrigel is mixed with a polypeptide of the invention at 150 ng/ml at 4 degrees C and drawn into cold 3 ml syringes. Female C57Bl/6 mice approximately 8 weeks old are injected with the mixture of Matrigel and experimental protein at 2 sites at the midventral aspect of the abdomen (0.5 ml/site). After 7 days, the mice are sacrificed by cervical dislocation, the

Matrigel plugs are removed and cleaned (i.e., all clinging membranes and fibrous tissue is removed). Replicate whole plugs are fixed in neutral buffered 10% formaldehyde, embedded in paraffin and used to produce sections for histological examination after staining with Masson's Trichrome. Cross sections from 3 different regions of each plug are processed. Selected sections are stained for the presence of vWF. The positive control for this assay is bovine basic FGF (150 ng/ml). Matrigel alone is used to determine basal levels of angiogenesis.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 44: Rescue of Ischemia in Rabbit Lower Limb Model

To study the in vivo effects of polynucleotides and polypeptides of the invention on ischemia, a rabbit hindlimb ischemia model is created by surgical removal of one femoral arteries as described previously (Takeshita *et al.*, *Am J. Pathol* 147:1649-1660 (1995)). The excision of the femoral artery results in retrograde propagation of thrombus and occlusion of the external iliac artery. Consequently, blood flow to the ischemic limb is dependent upon collateral vessels originating from the internal iliac artery (Takeshita *et al.* *Am J. Pathol* 147:1649-1660 (1995)). An interval of 10 days is allowed for post-operative recovery of rabbits and development of endogenous collateral vessels. At 10 day post-operatively (day 0), after performing a baseline angiogram, the internal iliac artery of the ischemic limb is transfected with 500 mg naked expression plasmid containing a polynucleotide of the invention by arterial gene transfer technology using a hydrogel-coated balloon catheter as described (Riessen *et al.* *Hum Gene Ther.* 4:749-758 (1993); Leclerc *et al.* *J. Clin. Invest.* 90: 936-944 (1992)). When a polypeptide of the invention is used in the treatment, a single bolus of 500 mg polypeptide of the invention or control is delivered into the internal iliac artery of the ischemic limb over a period of 1 min. through an infusion catheter. On day 30, various parameters are measured in these rabbits: (a) BP ratio - The blood pressure ratio of systolic pressure of the ischemic limb to that of normal limb; (b) Blood Flow and Flow Reserve - Resting FL: the blood flow

during undilated condition and Max FL: the blood flow during fully dilated condition (also an indirect measure of the blood vessel amount) and Flow Reserve is reflected by the ratio of max FL: resting FL; (c) Angiographic Score - This is measured by the angiogram of collateral vessels. A score is determined by the percentage of circles in an overlaying grid that with crossing opacified arteries divided by the total number in the rabbit thigh; (d) Capillary density - The number of collateral capillaries determined in light microscopic sections taken from hindlimbs.

The studies described in this example tested activity of polynucleotides and polypeptides of the invention. However, one skilled in the art could easily modify the exemplified studies to test the agonists, and/or antagonists of the invention.

Example 45: Effect of Polypeptides of the Invention on Vasodilation

Since dilation of vascular endothelium is important in reducing blood pressure, the ability of polypeptides of the invention to affect the blood pressure in spontaneously hypertensive rats (SHR) is examined. Increasing doses (0, 10, 30, 100, 300, and 900 mg/kg) of the polypeptides of the invention are administered to 13-14 week old spontaneously hypertensive rats (SHR). Data are expressed as the mean \pm SEM. Statistical analysis are performed with a paired t-test and statistical significance is defined as $p < 0.05$ vs. the response to buffer alone.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 46: Rat Ischemic Skin Flap Model

The evaluation parameters include skin blood flow, skin temperature, and factor VIII immunohistochemistry or endothelial alkaline phosphatase reaction. Expression of polypeptides of the invention, during the skin ischemia, is studied using in situ hybridization.

The study in this model is divided into three parts as follows:

- a) Ischemic skin
- b) Ischemic skin wounds
- c) Normal wounds

The experimental protocol includes:

- 5 a) Raising a 3x4 cm, single pedicle full-thickness random skin flap (myocutaneous flap over the lower back of the animal).
- b) An excisional wounding (4-6 mm in diameter) in the ischemic skin (skin-flap).
- c) Topical treatment with a polypeptide of the invention of the excisional wounds (day 0, 1, 2, 3, 4 post-wounding) at the following various dosage ranges: 1mg to 100 mg.
- 10 d) Harvesting the wound tissues at day 3, 5, 7, 10, 14 and 21 post-wounding for histological, immunohistochemical, and in situ studies.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the
15 invention.

Example 47: Peripheral Arterial Disease Model

Angiogenic therapy using a polypeptide of the invention is a novel therapeutic
20 strategy to obtain restoration of blood flow around the ischemia in case of peripheral arterial diseases. The experimental protocol includes:

- a) One side of the femoral artery is ligated to create ischemic muscle of the hindlimb, the other side of hindlimb serves as a control.
- b) a polypeptide of the invention, in a dosage range of 20 mg - 500 mg, is
25 delivered intravenously and/or intramuscularly 3 times (perhaps more) per week for 2-3 weeks.
- c) The ischemic muscle tissue is collected after ligation of the femoral artery at 1, 2, and 3 weeks for the analysis of expression of a polypeptide of the invention and histology. Biopsy is also performed on the other side of normal muscle of the
30 contralateral hindlimb.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to

test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 48: Ischemic Myocardial Disease Model

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A polypeptide of the invention is evaluated as a potent mitogen capable of stimulating the development of collateral vessels, and restructuring new vessels after coronary artery occlusion. Alteration of expression of the polypeptide is investigated in situ. The experimental protocol includes:

10 a) The heart is exposed through a left-side thoracotomy in the rat. Immediately, the left coronary artery is occluded with a thin suture (6-0) and the thorax is closed.

b) a polypeptide of the invention, in a dosage range of 20 mg - 500 mg, is delivered intravenously and/or intramuscularly 3 times (perhaps more) per week for 2-4 weeks.

15 c) Thirty days after the surgery, the heart is removed and cross-sectioned for morphometric and in situ analyzes.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the
20 invention.

Example 49: Rat Corneal Wound Healing Model

This animal model shows the effect of a polypeptide of the invention on
25 neovascularization. The experimental protocol includes:

a) Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.

b) Inserting a spatula below the lip of the incision facing the outer corner of the eye.

30 c) Making a pocket (its base is 1-1.5 mm from the edge of the eye).

d) Positioning a pellet, containing 50ng- 5ug of a polypeptide of the invention, within the pocket.

e) Treatment with a polypeptide of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 50: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing

Models

A. Diabetic db+/db+ Mouse Model.

To demonstrate that a polypeptide of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al.*, *J. Surg. Res.* 52:389 (1992); Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al.* *Proc. Natl. Acad. Sci. USA* 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol.* 120:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol.* 51(1):1-7 (1983); Leiter *et al.*, *Am. J. of Pathol.* 114:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol.* 83(2):221-232 (1984); Robertson *et al.*, *Diabetes* 29(1):60-67 (1980); Giacomelli *et al.*, *Lab Invest.* 40(4):460-473 (1979); Coleman, D.L., *Diabetes* 31 (Suppl):1-6 (1982)). These

homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol.* 120:1375-1377 (1978)).

The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol.* 136:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med.* 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water.. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

A polypeptide of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

5 Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

15 Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with a polypeptide of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

25 Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

30 Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer can serve as a positive tissue control and human brain tissue can be used as a negative tissue control. Each specimen includes a section with omission of the primary

antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is
5 considered significant.

B. Steroid Impaired Rat Model

The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-
10 Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahlet *et al.*, *J. Immunol.* 115: 476-481 (1975); Werb *et al.*, *J. Exp. Med.* 147:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *An. Intern. Med.* 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*,
15 *J. Clin. Invest.* 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al.*, *Growth*
20 *Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2229-2233 (1989)).

To demonstrate that a polypeptide of the invention can accelerate the healing
25 process, the effects of multiple topical applications of the polypeptide on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and
30 are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad*

libitum. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

5 The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue
10 punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

 Wounds are visually examined and photographed at a fixed distance at the day of
15 wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

 The polypeptide of the invention is administered using at a range different doses,
20 from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

 Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue
25 cassettes between biopsy sponges for further processing.

 Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

 Wound closure is analyzed by measuring the area in the vertical and horizontal
30 axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8).

The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

5

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with a polypeptide of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

15 The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

20 **Example 51: Lymphadema Animal Model**

or The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of a polypeptide of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

30 Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing.

Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of
5 dye into paws.

Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main
10 lymphatic vessels in this area are then electrically coagulated suture ligated.

Using a microscope, muscles in back of the leg (near the semitendinosus and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and ligated by suturing. The popliteal lymph node, and any accompanying adipose
15 tissue, is then removed by cutting connective tissues.

Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond). (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying
20 muscle when necessary.

To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated
25 places on each paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

Circumference Measurements: Under brief gas anesthetic to prevent limb
30 movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are taken from both control and edematous limbs.

Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then
5 dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and Ca^{2+} comparison.

10 Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

Histological Preparations: The transverse muscle located behind the knee
15 (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to
20 test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

**Example 52: Suppression of TNF alpha-induced adhesion molecule expression
by a Polypeptide of the Invention**

25 The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and
30 endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and

extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

5 Tumor necrosis factor alpha (TNF- α), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of a polypeptide of the invention to mediate a suppression of TNF- α induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF- α treated ECs when co-stimulated with a member of the FGF family of proteins.

To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO₂.

15 HUVECs are seeded in 96-well plates at concentrations of 1×10^4 cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for

20 CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 μ l of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 μ l volumes). Plates are incubated at 37 degree C for

25 either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μ l of 0.1% paraformaldehyde-PBS(with Ca⁺⁺ and Mg⁺⁺) is added to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 μ l of

30 diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μ g/ml (1:10 dilution

of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20 µl of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with
5 PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5
10 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNPP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [
15 5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the
20 invention.

Example 53: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation

This assay is based on the ability of human CD34+ to proliferate in the
25 presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range
30 of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone

has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL-3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5×10^5 cells/ml. During this time, 100 μ l of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10 μ l of prepared cytokines, 50 μ l SID (supernatants at 1:2 dilution = 50 μ l) and 20 μ l of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100 μ l. The plates are then placed in a 37°C/5% CO₂ incubator for five days.

Eighteen hours before the assay is harvested, 0.5 μ Ci/well of [3H] Thymidine is added in a 10 μ l volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 μ l Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film. A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined

via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell proliferation and/or to decrease the inhibition of cell proliferation in the presence of cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

Example 54: Assay for Extracellular Matrix Enhanced Cell Response (EMECCR)

The objective of the Extracellular Matrix Enhanced Cell Response (EMECCR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the $\alpha_5\beta_1$ and $\alpha_4\beta_1$ integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and responsible for stimulating

stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of $0.2 \mu\text{g}/\text{cm}^2$. Mouse bone marrow cells are
5 plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Gene products are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent
10 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5% CO_2 , 7% O_2 , and 88% N_2) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization
15 of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

20 If a particular gene product is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The gene product may
25 also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be
30 employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses

of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

Example 55: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation

The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNF α stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 μ l culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 μ g/ml hEGF, 5mg/ml insulin, 1 μ g/ml hFGF, 50mg/ml gentamycin, 50 μ g/ml Amphotericin B, 5%FBS. After incubation @ 37°C for at least 4-5 hours culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for

AoSMC contains SM basal media, 50mg/ml gentamycin, 50µg/ml Amphotericin B, 0.4% FBS. Incubate at 37C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed which should always include media controls and known-protein controls.

- 5 For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFa is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Then add 1/3 vol media containing controls or supernatants and incubate at 37C/5% CO₂ until day 5.

- 10 Transfer 60µl from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4C until Day 6 (for IL6 ELISA). To the remaining 100 µl in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10µl). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

- 15 On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 µl/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

- On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 µl/well of
20 Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 µl/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker.

- 25 Wash plates with wash buffer and blot on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 µl/well. Cover the plate and incubate 1 h at RT. Wash plates with wash buffer. Blot on paper towels.

- Add 100 µl/well of Enhancement Solution. Shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each
30 assay were tabulated and averaged.

A positive result in this assay suggests AoSMC cell proliferation and that the gene product of interest may be involved in dermal fibroblast proliferation and/or

smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the gene/gene product of interest. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the gene product and polynucleotides of the gene may be used in wound healing and dermal regeneration, as well as the promotion of vasculargenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides of the gene product and polynucleotides of the gene may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides of the gene product and polynucleotides of the gene may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 56: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells

The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 μ l of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 μ l volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μ l of 0.1% paraformaldehyde-PBS(with Ca⁺⁺ and Mg⁺⁺) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10 μ l of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μ g/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 μ l of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 μ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of

the ExtrAvidin-Alkaline Phosphatase in glycine buffer: $1:5,000 (10^0) > 10^{-0.5} > 10^{-1} > 10^{-1.5}$. 5 μ l of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μ l of pNPN reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 μ l of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

10

Example 57: Alamar Blue Endothelial Cells Proliferation Assay

This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration.

15 Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days.

25 After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The

30

plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

Example 58: Detection of Inhibition of a Mixed Lymphocyte Reaction

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM[®], density 1.0770 g/ml,

Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2×10^6 cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2×10^5 cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50 μ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 μ g/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10 μ g/ml. Cells are cultured for 7-8 days at 37°C in 5% CO₂, and 1 μ C of [³H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both incorporated herein by reference in their entireties. Additionally, the content of U.S. provisional application Serial No. 60/155,709 is hereby incorporated by reference in its entirety.

Table 7

	Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
5	Met	1	.	.	B	0.12	0.04	*	.	.	-0.10	0.18
	Glu	2	.	.	B	0.62	-0.39	*	.	.	0.50	0.28
	Cys	3	.	.	B	0.42	-0.81	*	.	.	1.10	0.43
	Cys	4	.	.	B	0.50	-0.74	*	.	.	1.40	0.44
	Arg	5	T	.	.	0.68	-0.87	*	.	.	2.10	0.37
10	Arg	6	T	.	.	0.93	-0.44	*	.	F	2.40	1.06
	Ala	7	T	.	.	0.62	-0.59	*	.	F	3.00	1.96
	Thr	8	T	C	0.48	-0.67	.	.	F	2.70	1.45
	Pro	9	T	T	.	0.33	0.01	*	.	F	1.55	0.61
	Gly	10	T	T	.	-0.59	0.70	*	.	F	0.95	0.50
15	Thr	11	.	.	B	.	.	T	.	-1.40	0.89	.	*	F	0.25	0.28
	Leu	12	.	A	B	-1.62	1.19	.	.	.	-0.60	0.16
	Leu	13	.	A	B	-1.90	1.44	.	.	.	-0.60	0.13
	Leu	14	.	A	B	-2.39	1.51	.	.	.	-0.60	0.09
	Phe	15	.	A	B	-2.86	1.81	.	.	.	-0.60	0.10
20	Leu	16	.	A	B	-3.36	1.81	.	.	.	-0.60	0.10
	Ala	17	.	A	B	-3.36	1.81	.	.	.	-0.60	0.10
	Phe	18	.	A	B	-2.84	1.81	.	.	.	-0.60	0.09
	Leu	19	.	A	B	-2.33	1.41	.	*	.	-0.60	0.15
	Leu	20	.	A	B	-1.52	1.11	.	.	.	-0.60	0.20
25	Leu	21	.	A	B	-1.02	0.61	.	.	.	-0.60	0.45
	Ser	22	T	C	-1.02	0.31	*	.	F	0.45	0.79
	Ser	23	T	C	-0.21	0.13	*	.	F	0.45	0.97
	Arg	24	T	C	0.30	-0.56	*	.	F	1.50	2.30
	Thr	25	T	C	1.11	-0.86	*	.	F	1.50	2.30
30	Ala	26	.	A	C	1.92	-1.24	*	.	F	1.10	2.98
	Arg	27	.	A	C	2.22	-1.63	*	.	F	1.44	2.63
	Ser	28	.	A	B	2.63	-1.63	*	.	F	1.58	3.04
	Glu	29	.	A	B	2.52	-2.11	*	.	F	1.92	5.90
	Glu	30	.	A	B	2.49	-2.61	.	*	F	2.26	5.03
35	Asp	31	T	T	.	2.27	-2.19	.	.	F	3.40	3.72
	Arg	32	T	T	.	1.87	-1.89	.	.	F	3.06	1.77
	Asp	33	T	T	.	2.17	-0.97	.	.	F	2.72	1.07
	Gly	34	T	T	.	1.58	-0.97	.	.	F	2.38	1.07
	Leu	35	T	.	.	1.29	-0.47	.	.	.	1.24	0.55
40	Trp	36	C	0.94	0.44	.	.	.	-0.20	0.35
	Asp	37	C	0.62	0.87	*	.	.	-0.20	0.35
	Ala	38	T	.	.	0.33	0.87	*	.	.	0.00	0.65
	Trp	39	C	0.38	1.10	*	.	.	-0.20	0.65
	Gly	40	T	C	1.19	0.57	*	.	.	0.00	0.53
45	Pro	41	T	T	.	0.81	0.57	.	.	F	0.35	0.90
	Trp	42	T	T	.	0.51	0.64	*	.	F	0.66	0.46
	Ser	43	T	C	1.21	0.11	*	.	F	1.07	0.62
	Glu	44	T	.	.	1.19	-0.31	*	.	F	1.98	0.79
	Cys	45	T	T	.	0.87	-0.26	*	.	F	2.64	1.08
50	Ser	46	T	T	.	0.73	-0.60	*	.	F	3.10	0.43
	Arg	47	T	T	.	0.68	-0.56	*	.	F	2.79	0.25
	Thr	48	T	T	.	0.63	-0.13	*	.	F	2.18	0.46
	Cys	49	T	T	.	0.04	-0.27	*	.	F	1.87	0.34
	Gly	50	T	T	.	0.41	-0.16	*	.	F	1.56	0.17
55	Gly	51	T	T	.	0.47	0.23	.	.	F	0.65	0.16
	Gly	52	T	T	.	0.06	0.50	.	*	F	0.35	0.47
	Ala	53	T	C	-0.44	0.31	*	*	F	0.45	0.64
	Ser	54	.	.	B	.	.	T	.	0.33	0.57	*	.	.	-0.20	0.53
	Tyr	55	.	.	B	.	.	T	.	0.79	0.14	*	.	.	0.25	1.05
60	Ser	56	.	.	B	.	.	T	.	0.47	-0.29	*	*	.	0.85	2.04
	Leu	57	.	.	B	0.00	-0.21	*	.	.	0.50	0.82
	Arg	58	.	.	B	0.29	0.09	*	*	.	-0.10	0.43
	Arg	59	.	.	B	0.29	-0.29	*	*	.	0.50	0.43
	Cys	60	.	.	B	0.58	-0.29	*	*	.	0.84	0.70

5	Leu	61	T	.	.	0.58	-0.97	*	.	F	2.03	0.71
	Ser	62	T	.	.	0.72	-0.59	*	.	F	2.37	0.49
	Ser	63	T	T	.	0.61	-0.01	.	.	F	2.61	0.49
	Lys	64	T	T	.	0.16	-0.59	*	.	F	3.40	1.02
	Ser	65	T	T	.	0.93	-0.84	.	.	F	2.91	0.76
10	Cys	66	T	T	.	1.74	-1.23	.	.	F	3.06	1.11
	Glu	67	T	.	.	1.16	-1.21	*	.	F	2.71	0.89
	Gly	68	T	T	.	1.57	-0.53	*	.	F	2.91	0.46
	Arg	69	T	T	.	1.28	-0.91	.	*	F	3.06	1.70
	Asn	70	T	T	.	1.69	-0.73	.	*	F	3.40	1.54
15	Ile	71	.	.	B	.	.	T	.	2.04	-0.73	.	*	.	2.51	3.04
	Arg	72	.	.	B	1.38	-0.67	.	*	.	1.97	2.24
	Tyr	73	T	.	.	1.42	-0.10	.	*	.	1.89	0.75
	Arg	74	T	.	.	1.31	-0.11	.	*	.	2.01	1.43
	Thr	75	T	.	.	0.46	-0.40	.	*	F	2.13	1.17
20	Cys	76	T	T	.	1.34	0.24	.	*	F	1.89	0.56
	Ser	77	T	T	.	0.57	-0.51	.	*	F	3.10	0.47
	Asn	78	T	T	.	0.60	0.06	*	*	.	1.74	0.18
	Val	79	T	T	.	0.28	0.00	*	*	.	2.03	0.51
	Asp	80	T	.	.	0.59	-0.14	.	*	.	1.86	0.59
25	Cys	81	.	.	B	0.67	-0.53	.	*	F	1.94	0.63
	Pro	82	.	.	B	.	.	T	.	0.62	-0.43	*	*	F	1.87	0.86
	Pro	83	T	T	.	0.62	-0.64	.	*	F	2.91	0.51
	Glu	84	T	T	.	0.78	-0.64	.	*	F	3.40	1.58
	Ala	85	T	T	.	0.89	-0.43	.	*	F	2.61	0.89
30	Gly	86	T	.	.	0.97	-0.86	.	*	F	2.52	1.12
	Asp	87	.	A	.	.	T	.	.	1.18	-0.79	.	*	F	1.83	0.66
	Phe	88	.	A	B	1.39	-0.39	.	*	.	0.79	1.12
	Arg	89	.	A	B	0.72	-0.49	.	*	.	0.45	1.97
	Ala	90	.	A	B	1.01	-0.34	.	*	.	0.30	0.63
35	Gln	91	.	.	B	.	.	T	.	0.77	0.04	.	*	.	0.10	0.98
	Gln	92	.	.	B	.	.	T	.	0.73	-0.24	.	*	.	0.70	0.50
	Cys	93	T	T	.	1.43	0.26	.	*	.	0.50	0.68
	Ser	94	T	T	.	1.32	0.16	.	*	.	0.50	0.63
	Ala	95	T	.	.	1.06	-0.24	.	*	.	0.90	0.61
40	His	96	T	T	.	1.10	0.00	.	*	.	0.80	0.84
	Asn	97	T	T	.	1.07	-0.57	.	*	.	2.15	1.26
	Asp	98	T	T	.	1.70	-0.46	*	*	F	2.30	1.69
	Val	99	.	.	B	.	.	T	.	1.66	-0.46	*	*	F	2.20	1.69
	Lys	100	T	.	.	2.24	-0.53	*	*	F	3.00	1.04
45	His	101	T	C	1.58	-0.53	*	*	F	2.55	1.08
	His	102	T	C	1.33	0.26	*	*	.	1.35	1.26
	Gly	103	T	C	1.33	0.37	.	*	.	0.90	0.99
	Gln	104	.	.	B	.	.	T	.	1.90	0.37	*	*	.	0.55	1.26
	Phe	105	.	A	B	1.04	0.79	*	*	.	-0.60	0.97
50	Tyr	106	.	A	B	0.87	0.97	.	.	.	-0.60	0.81
	Glu	107	.	A	B	0.04	0.97	.	.	.	-0.60	0.72
	Trp	108	.	A	B	0.09	1.21	.	.	.	-0.60	0.62
	Leu	109	.	.	B	0.09	0.81	*	.	.	-0.40	0.53
	Pro	110	T	.	.	0.79	0.46	*	.	.	0.00	0.49
55	Val	111	T	.	.	0.82	0.46	.	.	.	0.34	0.78
	Ser	112	T	.	.	0.82	-0.03	.	.	F	1.88	1.46
	Asn	113	T	.	.	1.11	-0.71	.	.	F	2.52	1.58
	Asp	114	T	C	1.71	-0.74	.	.	F	2.86	3.43
	Pro	115	T	T	.	1.26	-0.96	*	.	F	3.40	3.95
60	Asp	116	T	T	.	1.81	-0.77	*	.	F	3.06	1.32
	Asn	117	T	C	1.30	-0.79	.	*	F	2.52	1.06
	Pro	118	T	.	.	1.34	-0.10	.	*	F	1.73	0.56
	Cys	119	.	A	.	.	T	.	.	0.68	-0.53	.	*	F	1.49	0.68
	Ser	120	.	A	B	0.89	0.04	.	*	.	-0.30	0.23
60	Leu	121	.	A	B	0.30	0.04	.	*	.	-0.30	0.25
	Lys	122	.	A	B	0.34	0.11	.	*	.	-0.30	0.48
	Cys	123	.	A	B	0.21	-0.46	.	*	.	0.55	0.71

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	Gln	124	.	A	B	.	.	.	0.57	-0.41	.	*	.	0.80	0.85
	Ala	125	.	.	B	.	.	T	0.56	-0.61	.	*	F	1.90	0.61
	Lys	126	.	.	B	.	.	T	0.56	-0.13	*	*	F	2.00	1.65
5	Gly	127	T	T	-0.34	-0.01	.	*	F	2.50	0.79
	Thr	128	.	.	B	.	.	T	-0.53	0.23	.	*	F	1.25	0.58
	Thr	129	.	A	B	B	.	.	-0.53	0.37	.	*	F	0.60	0.21
	Leu	130	.	A	B	B	.	.	-0.76	0.37	*	.	.	0.20	0.38
	Val	131	.	A	B	B	.	.	-1.39	0.63	*	.	.	-0.35	0.21
10	Val	132	.	A	B	B	.	.	-1.26	0.64	*	*	.	-0.60	0.15
	Glu	133	.	A	B	B	.	.	-0.90	0.59	*	*	.	-0.60	0.28
	Leu	134	.	A	B	.	.	.	-1.44	-0.10	*	*	.	0.30	0.76
	Ala	135	.	A	B	.	.	.	-1.44	-0.10	*	*	.	0.30	0.76
	Pro	136	.	A	B	.	.	.	-0.59	-0.06	*	.	F	0.45	0.36
15	Lys	137	.	A	B	.	.	.	-0.08	-0.06	*	*	F	0.45	0.73
	Val	138	.	A	B	.	.	.	-0.39	-0.31	*	.	F	0.45	0.72
	Leu	139	.	A	B	.	.	.	0.53	-0.33	*	.	F	0.45	0.67
	Asp	140	.	A	B	.	.	.	0.46	-0.76	*	.	F	0.75	0.66
	Gly	141	.	.	B	.	.	T	0.42	-0.19	*	.	F	0.85	0.47
20	Thr	142	.	.	B	.	.	T	0.07	-0.07	*	.	F	0.85	0.90
	Arg	143	.	.	B	.	.	T	0.92	-0.27	*	.	F	0.85	0.78
	Cys	144	.	.	B	.	.	T	1.43	-0.27	*	.	.	0.85	1.36
	Tyr	145	.	.	B	.	.	.	0.62	-0.31	*	.	.	0.65	1.26
	Thr	146	.	A	B	.	.	.	0.97	-0.11	*	.	F	0.45	0.53
25	Glu	147	.	A	B	.	.	.	0.68	-0.11	*	.	F	0.60	1.66
	Ser	148	.	A	B	.	.	.	-0.10	-0.07	*	*	F	0.60	1.05
	Leu	149	.	A	B	.	.	.	-0.32	-0.26	.	*	.	0.30	0.39
	Asp	150	.	A	.	.	T	.	-0.38	-0.06	*	*	.	0.70	0.16
	Met	151	.	A	B	.	.	.	-0.41	0.33	*	*	.	-0.30	0.16
30	Cys	152	.	.	B	.	.	T	-1.22	0.37	*	*	.	0.10	0.19
	Ile	153	.	.	B	.	.	T	-1.59	0.37	*	*	.	0.10	0.09
	Ser	154	.	.	B	.	.	T	-0.78	0.94	*	*	.	-0.20	0.05
	Gly	155	T	T	-1.67	0.73	*	*	.	0.20	0.16
	Leu	156	.	.	B	B	.	.	-1.92	0.84	*	.	.	-0.60	0.16
35	Cys	157	.	.	B	B	.	.	-1.60	0.80	*	.	.	-0.60	0.09
	Gln	158	.	.	B	B	.	.	-1.38	0.84	*	.	.	-0.60	0.09
	Ile	159	.	.	B	B	.	.	-1.08	0.99	.	.	.	-0.60	0.06
	Val	160	.	.	B	B	.	.	-0.77	0.30	.	.	.	-0.30	0.18
	Gly	161	.	.	B	.	.	.	0.04	0.23	*	.	.	-0.10	0.14
40	Cys	162	.	.	B	.	.	T	-0.10	0.23	.	.	.	0.10	0.36
	Asp	163	.	.	B	.	.	T	-0.44	0.23	.	.	.	0.10	0.39
	His	164	.	.	B	.	.	T	0.14	0.01	.	.	.	0.10	0.39
	Gln	165	T	T	0.69	-0.03	.	*	.	1.10	0.99
	Leu	166	.	.	B	B	.	.	0.18	-0.11	*	*	.	0.30	0.85
45	Gly	167	.	.	.	B	T	.	0.89	0.53	*	*	F	-0.05	0.47
	Ser	168	.	.	B	B	.	.	0.89	0.03	*	*	F	-0.15	0.54
	Thr	169	.	.	B	B	.	.	0.92	-0.37	*	*	F	0.94	1.13
	Val	170	.	.	B	B	.	.	0.92	-1.06	.	*	F	1.58	1.90
	Lys	171	.	.	B	B	.	.	1.07	-1.09	.	.	F	1.92	2.28
50	Glu	172	.	.	B	.	.	.	1.07	-0.90	.	.	F	2.31	0.85
	Asp	173	T	T	0.51	-0.96	.	.	F	3.40	1.13
	Asn	174	T	T	0.16	-0.96	.	.	F	2.91	0.42
	Cys	175	T	T	1.01	-0.39	*	.	.	2.12	0.13
55	Gly	176	.	.	B	.	.	T	0.62	0.01	.	.	.	0.78	0.13
	Val	177	.	.	B	.	.	.	0.62	0.44	.	.	.	-0.06	0.08
	Cys	178	.	.	B	.	.	.	0.28	0.04	.	.	.	-0.10	0.24
	Asn	179	T	T	-0.02	-0.10	.	.	F	1.56	0.24
	Gly	180	T	T	0.33	-0.14	.	.	F	1.87	0.43
60	Asp	181	T	T	0.01	-0.30	*	.	F	2.33	1.17
	Gly	182	T	T	0.98	-0.30	*	.	F	2.49	0.39
	Ser	183	T	T	0.83	-0.70	*	.	F	3.10	0.77
	Thr	184	.	.	B	.	.	T	-0.02	-0.44	*	.	F	2.09	0.38
	Cys	185	.	.	B	.	.	T	0.43	0.20	*	.	F	1.18	0.28
	Arg	186	.	.	B	.	.	T	0.09	-0.23	*	.	.	1.32	0.42

5	Leu	187	.	.	B	B	.	.	.	0.43	-0.19	*	.	.	0.61	0.29
	Val	188	.	.	B	B	.	.	.	0.49	-0.27	*	*	.	0.56	0.92
	Arg	189	.	.	B	B	.	.	.	0.84	-0.09	*	*	F	0.97	0.74
	Gly	190	T	.	.	1.21	-0.09	*	*	F	1.98	1.79
	Gln	191	T	.	.	1.10	-0.39	*	*	F	2.24	3.23
10	Tyr	192	.	.	B	.	.	T	.	1.10	-0.63	.	*	F	2.60	2.86
	Lys	193	.	.	B	.	.	T	.	1.66	0.06	.	*	F	1.44	2.38
	Ser	194	.	.	B	.	.	T	.	0.96	0.01	.	*	F	1.18	1.84
	Gln	195	.	.	B	.	.	T	.	0.99	0.11	.	*	F	0.92	1.19
	Leu	196	.	A	B	1.03	-0.16	.	*	F	0.71	0.86
15	Ser	197	.	A	B	0.98	-0.16	.	*	F	0.94	1.28
	Ala	198	.	A	B	0.93	-0.16	.	*	F	1.13	0.99
	Thr	199	.	A	B	1.23	-0.56	.	.	F	1.92	2.00
	Lys	200	.	A	.	.	T	.	.	0.92	-1.24	.	.	F	2.66	2.50
	Ser	201	T	T	.	0.88	-1.14	.	.	F	3.40	3.57
20	Asp	202	T	T	.	0.32	-1.00	.	.	F	3.06	1.84
	Asp	203	.	.	B	.	.	T	.	0.32	-0.84	*	.	F	2.17	0.68
	Thr	204	.	.	B	.	.	T	.	-0.26	-0.34	.	.	F	1.53	0.51
	Val	205	.	.	B	B	.	.	.	-0.51	-0.04	.	.	.	0.64	0.22
	Val	206	.	.	B	B	.	.	.	-0.46	0.39	.	.	.	-0.30	0.20
25	Ala	207	.	.	B	B	.	.	.	-0.80	1.14	.	.	.	-0.60	0.22
	Ile	208	.	.	B	.	.	T	.	-1.10	1.09	*	*	.	-0.20	0.29
	Pro	209	.	.	B	.	.	T	.	-0.68	0.83	.	.	.	-0.20	0.52
	Tyr	210	T	T	.	0.14	0.19	*	.	.	0.65	1.01
	Gly	211	T	T	.	0.11	0.19	*	*	F	0.80	1.96
30	Ser	212	.	.	B	0.81	0.19	*	*	F	0.05	0.89
	Arg	213	.	A	B	0.89	-0.24	*	*	F	0.60	1.11
	His	214	.	A	B	0.24	-0.31	*	*	.	0.30	0.93
	Ile	215	.	A	B	-0.32	-0.10	*	*	.	0.30	0.51
	Arg	216	.	A	B	0.07	0.20	*	*	.	-0.30	0.22
35	Leu	217	.	A	B	0.02	0.20	*	*	.	-0.30	0.32
	Val	218	.	A	B	-0.30	0.13	*	*	.	-0.30	0.45
	Leu	219	.	A	B	-0.27	-0.13	*	*	.	0.58	0.35
	Lys	220	.	A	C	0.59	-0.13	*	*	F	1.21	0.72
	Gly	221	T	C	-0.33	-0.31	*	*	F	2.04	1.31
40	Pro	222	T	C	0.23	-0.27	*	*	F	2.32	1.31
	Asp	223	T	T	.	0.28	-0.20	*	*	F	2.80	1.03
	His	224	.	.	B	.	.	T	.	1.09	0.49	.	*	.	0.92	0.86
	Leu	225	.	.	B	0.73	0.06	*	*	.	0.74	0.96
	Tyr	226	.	.	B	1.12	0.11	.	*	.	0.46	0.83
45	Leu	227	.	.	B	1.02	0.11	.	.	.	0.33	1.22
	Glu	228	.	.	B	0.21	0.10	*	.	F	0.20	2.14
	Thr	229	.	.	B	B	.	.	.	0.24	0.10	.	*	F	0.00	1.12
	Lys	230	.	.	B	B	.	.	.	0.71	-0.26	.	*	F	0.60	2.36
	Thr	231	.	.	B	B	.	.	.	0.64	-0.51	.	.	F	0.90	1.35
50	Leu	232	.	.	B	B	.	.	.	1.50	-0.03	.	.	F	0.60	1.35
	Gln	233	.	.	B	B	.	.	.	1.16	-0.51	.	.	F	1.20	1.35
	Gly	234	.	.	.	B	.	.	C	1.47	-0.09	.	.	F	1.25	0.93
	Thr	235	C	1.42	-0.57	.	.	F	2.20	1.94
	Lys	236	C	1.43	-0.86	.	.	F	2.50	1.80
55	Gly	237	T	.	C	1.43	-0.87	.	.	F	3.00	2.44
	Glu	238	.	.	B	.	T	.	.	1.13	-0.61	*	.	F	2.50	1.40
	Asn	239	T	C	.	1.18	-0.71	*	.	F	2.25	0.94
	Ser	240	T	C	.	1.18	-0.33	*	*	F	1.80	1.27
	Leu	241	.	.	B	0.79	-0.27	*	*	F	1.10	1.06
60	Ser	242	C	0.82	0.16	.	.	F	0.25	0.65
	Ser	243	T	C	0.12	0.24	*	.	F	0.45	0.70
	Thr	244	.	.	B	.	T	T	.	-0.69	0.64	*	.	F	0.35	0.73
	Gly	245	.	.	B	.	T	.	.	-1.24	0.64	*	*	F	-0.05	0.45
	Thr	246	.	.	B	.	T	.	.	-0.43	0.90	*	.	F	-0.05	0.25
	Phe	247	.	.	B	B	.	.	.	-0.13	0.51	.	.	.	-0.60	0.29
	Leu	248	.	.	B	B	.	.	.	-0.13	0.43	.	.	.	-0.60	0.47
	Val	249	.	.	B	B	.	.	.	-0.12	0.39	.	.	F	-0.15	0.44

595

5	Asp	250	.	.	B	.	.	T	.	-0.63	0.29	.	.	F	0.25	0.68
	Asn	251	T	C	-0.32	0.14	.	*	F	0.45	0.61
	Ser	252	T	C	-0.32	-0.54	.	*	F	1.50	1.37
	Ser	253	T	C	0.49	-0.40	*	.	F	1.05	0.71
	Val	254	.	.	B	1.39	0.00	*	.	F	0.65	0.77
10	Asp	255	.	.	B	0.69	-0.40	*	.	.	0.95	1.14
	Phe	256	.	.	B	0.48	0.00	*	*	.	1.10	0.74
	Gln	257	.	.	B	0.78	0.04	*	.	.	0.95	1.54
	Lys	258	.	.	B	1.12	-0.60	*	.	F	2.30	1.54
	Phe	259	T	C	1.98	-0.60	*	.	F	3.00	3.55
15	Pro	260	T	C	1.09	-1.39	*	.	F	2.70	3.55
	Asp	261	T	T	.	0.98	-1.10	*	*	F	2.60	1.24
	Lys	262	T	C	1.09	-0.41	*	*	F	1.80	1.19
	Glu	263	.	A	B	0.44	-1.20	*	*	F	1.20	1.50
	Ile	264	.	A	B	0.56	-1.01	*	*	.	0.60	0.89
20	Leu	265	.	A	B	0.42	-0.51	*	.	.	0.60	0.45
	Arg	266	.	A	B	0.21	-0.09	*	*	.	0.30	0.26
	Met	267	.	A	B	-0.64	0.34	*	*	.	-0.30	0.57
	Ala	268	.	A	B	-0.96	0.34	*	*	.	-0.30	0.57
	Gly	269	T	C	-0.66	0.14	*	*	.	0.30	0.42
25	Pro	270	T	C	0.16	0.64	*	*	F	0.15	0.43
	Leu	271	T	C	-0.66	0.03	*	*	.	0.30	0.70
	Thr	272	.	.	B	.	.	T	.	-0.94	0.31	.	*	.	0.10	0.62
	Ala	273	.	.	B	B	.	.	.	-1.21	0.57	*	*	.	-0.60	0.28
	Asp	274	.	.	B	B	.	.	.	-0.82	0.79	*	*	.	-0.60	0.25
30	Phe	275	.	.	B	B	.	.	.	-1.50	0.10	*	*	.	-0.30	0.35
	Ile	276	.	.	B	B	.	.	.	-0.58	0.30	*	*	.	-0.30	0.24
	Val	277	.	.	B	B	.	.	.	-0.27	-0.20	*	*	.	0.30	0.28
	Lys	278	.	.	B	B	.	.	.	0.02	0.20	*	*	.	-0.30	0.53
	Ile	279	.	.	B	B	.	.	.	-0.32	-0.20	*	*	F	0.90	1.01
35	Arg	280	.	.	B	B	.	.	.	0.08	-0.46	*	*	F	1.20	1.34
	Asn	281	T	T	.	0.38	-0.71	.	*	F	2.45	0.90
	Ser	282	T	C	1.23	-0.21	.	*	F	2.40	1.30
	Gly	283	T	C	0.89	-0.90	.	*	F	3.00	1.11
	Ser	284	T	C	1.47	-0.51	*	*	F	2.55	0.92
40	Ala	285	C	0.50	-0.43	*	*	F	1.75	0.99
	Asp	286	.	.	.	B	.	.	C	0.50	-0.17	.	*	F	1.25	0.74
	Ser	287	.	.	B	B	.	.	.	0.10	-0.20	*	*	F	0.75	0.96
	Thr	288	.	.	B	B	.	.	.	-0.44	0.20	*	*	F	-0.15	0.82
	Val	289	.	.	B	B	.	.	.	-0.84	0.39	*	*	.	-0.30	0.35
45	Gln	290	.	.	B	B	.	.	.	-0.50	1.17	.	*	.	-0.60	0.22
	Phe	291	.	.	B	B	.	.	.	-0.50	1.54	.	*	.	-0.60	0.24
	Ile	292	.	.	B	B	.	.	.	-0.41	1.46	.	.	.	-0.60	0.57
	Phe	293	.	.	B	B	.	.	.	-0.99	1.24	.	.	.	-0.60	0.51
	Tyr	294	.	.	B	B	.	.	.	-1.02	1.53	.	.	.	-0.60	0.41
50	Gln	295	.	.	B	B	.	.	.	-1.06	1.43	.	.	.	-0.60	0.41
	Pro	296	.	.	B	B	.	.	.	-0.24	1.24	*	.	.	-0.60	0.64
	Ile	297	.	.	.	B	T	.	.	0.36	0.46	*	*	.	-0.20	0.80
	Ile	298	.	.	.	B	.	.	C	1.17	0.61	*	*	.	-0.40	0.49
	His	299	.	.	.	B	.	.	C	1.41	0.21	*	*	.	0.20	0.62
55	Arg	300	.	.	.	B	T	.	.	1.10	-0.21	*	*	.	1.45	1.53
	Trp	301	.	.	.	B	T	.	.	1.31	-0.41	.	*	.	1.75	3.14
	Arg	302	.	.	.	B	T	.	.	1.50	-1.10	.	*	F	2.50	3.86
	Glu	303	T	.	.	1.69	-0.81	.	.	F	3.00	1.71
	Thr	304	T	.	.	1.51	-0.03	.	*	F	2.40	1.41
60	Asp	305	T	.	.	0.73	-0.51	.	*	F	2.40	1.11
	Phe	306	T	.	.	0.72	0.06	*	.	.	0.90	0.34
	Phe	307	T	C	0.02	0.44	*	.	.	0.30	0.32
	Pro	308	T	T	.	-0.29	0.46	.	.	.	0.20	0.19
	Cys	309	T	T	.	-0.64	0.94	.	.	.	0.20	0.32
	Ser	310	T	T	.	-0.99	0.73	.	.	.	0.20	0.20
	Ala	311	T	.	.	-0.63	0.37	.	.	.	0.30	0.13
	Thr	312	T	.	.	-0.28	0.37	.	.	.	0.30	0.24

	Cys	313	T	T	.	-0.31	0.23	.	.	F	0.65	0.17
	Gly	314	T	T	.	0.36	0.60	.	.	F	0.35	0.27
	Gly	315	T	T	.	-0.16	0.50	.	.	F	0.35	0.32
	Gly	316	T	T	.	0.12	0.70	.	.	F	0.35	0.50
5	Tyr	317	.	.	B	B	.	.	.	0.13	0.61	.	.	.	-0.60	0.73
	Gln	318	.	.	B	B	.	.	.	0.21	0.57	.	.	.	-0.60	0.98
	Leu	319	.	.	B	B	.	.	.	0.56	0.64	.	.	.	-0.45	1.00
	Thr	320	.	.	B	B	.	.	.	0.23	0.21	.	.	.	-0.15	1.11
10	Ser	321	.	.	B	B	.	.	.	0.33	0.03	.	.	F	-0.15	0.34
	Ala	322	.	.	B	0.58	0.39	.	.	.	-0.10	0.65
	Glu	323	.	.	B	-0.23	-0.30	.	*	.	0.50	0.75
	Cys	324	.	.	B	.	.	T	.	0.69	-0.10	.	*	.	1.04	0.46
	Tyr	325	.	.	B	.	.	T	.	0.70	-0.49	.	*	.	1.38	0.90
15	Asp	326	T	T	.	1.00	-0.60	.	.	.	2.42	0.70
	Leu	327	T	T	.	1.70	-0.20	.	.	.	2.61	2.09
	Arg	328	T	T	.	0.84	-0.77	*	.	F	3.40	2.61
	Ser	329	T	T	.	0.66	-0.89	.	*	F	3.06	1.16
	Asn	330	T	T	.	0.31	-0.24	*	*	F	2.42	1.04
20	Arg	331	.	.	B	.	.	T	.	0.31	-0.43	*	*	F	1.53	0.54
	Val	332	.	.	B	1.12	-0.43	*	.	.	0.84	0.67
	Val	333	.	.	B	0.77	-0.41	*	.	.	0.50	0.72
	Ala	334	.	.	B	0.40	-0.06	*	.	.	0.50	0.58
	Asp	335	.	.	B	.	.	T	.	0.37	0.51	*	.	.	-0.20	0.42
25	Gln	336	.	.	B	.	.	T	.	0.01	0.37	*	*	.	0.10	0.77
	Tyr	337	.	.	B	.	.	T	.	0.62	0.49	.	.	.	-0.05	1.19
	Cys	338	.	.	B	.	.	T	.	1.27	0.74	*	.	.	-0.05	1.11
	His	339	.	.	B	1.86	1.17	*	.	.	-0.40	0.99
	Tyr	340	.	.	B	1.86	0.77	*	.	.	-0.25	1.10
30	Tyr	341	.	.	B	.	.	T	.	0.97	0.41	*	.	.	-0.05	3.30
	Pro	342	T	T	.	1.26	0.53	*	*	.	0.35	1.70
	Glu	343	T	T	.	1.71	0.03	.	*	F	1.14	2.17
	Asn	344	T	T	.	1.79	-0.30	.	*	F	2.08	2.14
	Ile	345	T	.	.	1.82	-1.06	*	*	F	2.52	2.77
35	Lys	346	T	C	2.11	-1.06	*	*	F	2.86	2.47
	Pro	347	T	T	.	1.51	-1.06	.	*	F	3.40	3.07
	Lys	348	T	C	1.51	-0.77	.	*	F	2.86	3.62
	Pro	349	T	C	1.51	-1.06	.	*	F	2.52	3.13
	Lys	350	.	A	.	.	T	.	.	1.73	-1.06	.	*	F	1.98	3.51
40	Leu	351	.	A	B	1.69	-0.91	.	*	F	1.09	0.94
	Gln	352	.	A	B	1.09	-0.51	.	*	F	0.96	0.98
	Glu	353	.	A	B	1.04	-0.26	.	*	.	0.72	0.40
	Cys	354	.	A	B	1.04	-0.26	.	.	.	0.93	0.82
	Asn	355	.	A	.	.	T	.	.	0.33	-0.51	.	.	.	1.84	0.73
45	Leu	356	T	.	.	0.93	-0.34	.	.	F	2.10	0.23
	Asp	357	T	C	0.34	0.09	.	*	F	1.29	0.65
	Pro	358	T	T	.	0.46	0.01	.	*	F	1.28	0.41
	Cys	359	T	C	0.83	-0.39	*	*	F	1.47	0.97
	Pro	360	T	C	0.83	-0.16	.	*	.	1.11	0.61
50	Ala	361	.	A	.	.	T	.	.	1.06	-0.16	.	*	.	0.70	0.68
	Arg	362	.	A	B	0.74	-0.09	.	*	.	0.45	1.29
	Trp	363	.	A	B	0.74	-0.17	.	*	.	0.45	1.20
	Glu	364	.	A	B	1.12	-0.17	.	*	.	0.45	1.84
	Ala	365	.	A	.	.	T	.	C	1.02	0.24	.	*	.	0.10	0.99
55	Thr	366	.	A	C	1.02	0.73	.	*	F	-0.10	1.36
	Pro	367	.	A	.	.	T	.	.	0.24	0.31	.	*	F	0.25	0.79
	Trp	368	T	.	.	0.23	0.89	.	.	.	0.00	0.42
	Thr	369	T	T	.	-0.07	0.77	.	.	.	0.20	0.39
	Ala	370	T	T	.	0.22	0.67	.	.	.	0.20	0.34
60	Cys	371	T	T	.	-0.13	0.63	.	.	.	0.20	0.43
	Ser	372	T	T	.	-0.27	0.29	.	.	F	0.65	0.16
	Ser	373	T	.	.	-0.32	0.23	.	.	F	0.45	0.16
	Ser	374	T	.	.	-0.36	0.16	.	.	F	0.45	0.29
	Cys	375	T	T	.	-0.66	0.01	.	.	F	0.65	0.21

	Gly	376	T	T	.	0.01	0.31	.	.	F	0.65	0.11
	Gly	377	T	T	.	0.01	0.33	.	*	F	0.65	0.14
	Gly	378	T	T	.	0.42	0.33	.	*	F	0.65	0.36
5	Ile	379	.	.	B	B	.	.	.	0.13	-0.24	.	*	F	0.45	0.72
	Gln	380	.	.	B	B	.	.	.	-0.06	-0.17	.	*	F	0.45	0.73
	Ser	381	.	.	B	B	.	.	.	-0.01	0.04	.	*	F	-0.15	0.55
	Arg	382	.	.	B	B	.	.	.	-0.33	0.00	*	*	F	0.60	1.05
	Ala	383	.	.	B	B	.	.	.	-0.84	-0.11	*	*	.	0.30	0.32
10	Val	384	.	.	B	B	.	.	.	0.04	0.13	*	*	.	-0.30	0.18
	Ser	385	.	.	B	B	.	.	.	0.04	-0.26	*	*	.	0.30	0.16
	Cys	386	.	.	B	B	.	.	.	0.34	-0.26	*	*	.	0.56	0.27
	Val	387	.	.	B	B	.	.	.	-0.66	-0.76	*	*	.	1.12	0.61
	Glu	388	.	.	B	B	.	.	.	-0.07	-0.71	*	*	F	1.53	0.32
	Glu	389	.	.	B	0.44	-0.70	*	*	F	2.14	1.03
15	Asp	390	.	.	.	B	T	.	.	0.71	-0.84	*	*	F	2.60	1.38
	Ile	391	.	.	B	B	.	.	.	0.52	-0.99	*	*	F	1.94	1.08
	Gln	392	.	.	.	B	T	.	.	1.07	-0.34	*	*	F	1.63	0.46
	Gly	393	.	.	.	B	.	.	C	0.77	0.14	*	*	F	0.57	0.40
20	His	394	.	.	.	B	.	.	C	-0.09	0.53	*	*	.	-0.14	0.77
	Val	395	.	.	.	B	.	.	C	-0.09	0.49	*	*	.	-0.40	0.33
	Thr	396	.	.	.	B	.	.	C	0.80	0.09	*	*	F	0.05	0.58
	Ser	397	.	A	C	0.51	-0.34	.	.	F	0.65	0.73
	Val	398	.	A	B	0.90	0.07	.	.	F	0.00	1.04
25	Glu	399	.	A	.	.	T	.	.	0.27	-0.57	.	.	F	1.30	1.44
	Glu	400	.	A	.	.	T	.	.	0.52	-0.49	.	.	F	0.85	0.58
	Trp	401	.	A	.	.	T	.	.	0.59	-0.26	.	.	.	0.70	0.77
	Lys	402	.	A	.	.	T	.	.	0.58	-0.14	.	.	.	0.70	0.69
	Cys	403	.	A	.	.	T	.	.	1.22	0.34	.	*	.	0.10	0.58
30	Met	404	.	A	.	.	T	.	.	1.27	0.77	.	*	.	-0.20	0.85
	Tyr	405	.	A	.	.	T	.	.	0.67	-0.14	.	*	.	0.70	0.85
	Thr	406	T	C	0.74	0.47	.	*	.	0.15	1.57
	Pro	407	T	T	.	-0.19	0.33	.	*	F	0.80	2.45
	Lys	408	T	T	.	-0.11	0.40	.	.	F	0.80	1.10
35	Met	409	.	.	B	.	.	T	.	0.49	0.14	.	.	.	0.10	0.77
	Pro	410	.	.	B	0.52	0.06	.	.	.	-0.10	0.86
	Ile	411	.	.	B	0.17	0.06	.	.	.	-0.10	0.67
	Ala	412	.	.	B	0.38	0.63	.	*	.	-0.40	0.36
	Gln	413	.	.	B	.	.	T	.	-0.56	0.41	*	.	.	-0.20	0.37
40	Pro	414	.	.	B	.	.	T	.	-0.66	0.67	*	.	.	-0.20	0.37
	Cys	415	.	.	B	.	.	T	.	-0.44	0.77	*	.	.	-0.20	0.32
	Asn	416	.	.	B	.	.	T	.	-0.22	0.27	*	.	.	0.10	0.31
	Ile	417	.	.	B	0.16	0.44	.	.	.	-0.40	0.11
	Phe	418	.	.	B	0.20	0.44	.	.	.	-0.40	0.31
45	Asp	419	T	.	.	0.12	-0.13	*	.	.	0.90	0.39
	Cys	420	.	.	B	.	.	T	.	-0.02	0.39	*	.	.	0.10	0.58
	Pro	421	T	T	.	-0.61	0.39	*	.	.	0.50	0.55
	Lys	422	T	T	.	0.28	0.10	*	.	.	0.50	0.33
	Trp	423	T	T	.	0.98	0.50	*	.	.	0.35	1.08
50	Leu	424	.	A	C	0.69	-0.07	*	.	.	0.65	1.20
	Ala	425	.	A	.	.	T	.	.	1.06	0.41	*	.	.	-0.20	0.63
	Gln	426	.	A	.	.	T	.	.	1.06	0.80	*	.	.	-0.20	0.81
	Glu	427	.	A	.	.	T	.	.	0.34	0.31	*	.	.	0.25	1.51
	Trp	428	.	A	.	.	T	.	.	0.32	0.20	.	.	F	0.25	0.80
55	Ser	429	T	C	0.28	0.19	.	.	F	0.45	0.67
	Pro	430	T	T	.	0.56	0.43	.	.	F	0.35	0.29
	Cys	431	T	T	.	-0.11	0.91	.	.	.	0.20	0.39
	Thr	432	.	.	B	.	.	T	.	-0.46	0.57	.	.	.	-0.20	0.16
	Val	433	.	.	B	B	.	.	.	-0.17	0.61	.	.	.	-0.60	0.10
60	Thr	434	.	.	B	B	.	.	.	-0.21	0.59	.	.	.	-0.60	0.33
	Cys	435	.	.	B	B	.	.	.	-0.81	0.44	*	.	F	-0.45	0.22
	Gly	436	T	T	.	-0.03	0.64	*	*	F	0.35	0.25
	Gln	437	.	.	B	.	.	T	.	0.03	0.00	.	*	F	0.85	0.34
	Gly	438	T	T	.	1.00	0.27	.	*	F	0.65	0.98

	Leu	439	.	.	B	.	T	.	0.46	-0.30	.	*	.	0.85	1.95
	Arg	440	.	.	B	B	.	.	0.27	-0.09	.	*	.	0.30	0.83
	Tyr	441	.	.	B	B	.	.	-0.20	0.16	.	*	.	-0.30	0.63
5	Arg	442	.	.	B	B	.	.	-0.87	0.41	.	*	.	-0.60	0.63
	Val	443	.	.	B	B	.	.	-1.41	0.30	.	*	.	-0.30	0.17
	Val	444	.	.	B	B	.	.	-0.60	0.99	.	*	.	-0.60	0.08
	Leu	445	.	.	B	B	.	.	-0.74	0.23	.	*	.	-0.30	0.07
	Cys	446	.	.	B	B	.	.	-0.39	0.73	*	*	.	-0.35	0.12
	Ile	447	.	.	B	B	.	.	-0.84	0.09	*	*	.	0.20	0.32
10	Asp	448	.	.	B	.	T	.	-0.59	-0.13	*	*	.	1.45	0.38
	His	449	T	T	0.23	-0.20	*	*	.	2.10	0.70
	Arg	450	T	T	0.73	-0.27	*	*	.	2.50	1.36
	Gly	451	T	T	1.06	-0.47	.	*	.	2.25	1.18
	Met	452	T	.	1.60	-0.04	.	*	.	1.65	0.85
15	His	453	T	T	0.93	-0.11	.	.	.	1.60	0.43
	Thr	454	T	T	0.67	0.46	*	.	F	0.60	0.23
	Gly	455	T	T	0.34	0.41	*	.	F	0.69	0.32
	Gly	456	T	T	0.73	0.23	.	.	F	1.33	0.36
	Cys	457	T	.	1.02	-0.27	.	*	F	2.07	0.50
20	Ser	458	T	1.10	-0.27	.	*	F	2.41	0.73
	Pro	459	T	T	1.20	-0.70	.	*	F	3.40	1.47
	Lys	460	T	T	1.51	-0.70	.	*	F	3.06	4.24
	Thr	461	T	0.97	-0.77	.	*	F	2.52	4.30
	Lys	462	1.68	-0.47	.	*	F	1.68	1.95
25	Pro	463	1.98	-0.90	.	*	F	1.64	1.95
	His	464	.	A	.	.	T	.	2.19	-0.90	.	*	F	1.30	2.34
	Ile	465	.	A	B	.	.	.	1.48	-1.39	.	*	F	0.90	2.03
	Lys	466	.	A	B	.	.	.	0.90	-0.81	.	*	F	0.75	0.70
30	Glu	467	.	A	B	.	.	.	0.00	-0.56	.	*	F	0.75	0.36
	Glu	468	.	A	B	B	.	.	0.00	-0.41	.	*	.	0.30	0.38
	Cys	469	.	A	B	B	.	.	-0.28	-0.67	.	*	.	0.60	0.30
	Ile	470	.	A	B	B	.	.	0.40	-0.19	.	.	.	0.30	0.25
	Val	471	.	A	B	B	.	.	-0.31	0.24	.	.	.	-0.30	0.22
	Pro	472	.	A	B	B	.	.	-0.56	0.81	.	.	F	-0.45	0.22
35	Thr	473	.	.	B	.	.	T	-0.51	1.00	.	.	F	-0.05	0.49
	Pro	474	T	T	-0.06	0.31	.	*	F	0.80	1.33
	Cys	475	T	T	0.88	0.10	.	.	F	0.80	1.33
	Tyr	476	T	T	1.73	-0.33	.	*	F	1.40	1.84
	Lys	477	.	A	1.99	-0.81	*	*	F	1.10	2.06
40	Pro	478	.	A	.	.	T	.	1.49	-1.24	*	*	F	1.30	7.69
	Lys	479	.	A	.	.	T	.	1.49	-1.13	.	*	F	1.30	4.05
	Glu	480	.	A	B	.	.	.	1.30	-1.46	.	*	F	0.90	3.13
	Lys	481	.	A	B	.	.	.	1.54	-0.81	.	*	F	0.90	1.50
45	Leu	482	.	A	B	.	.	.	0.91	-1.24	.	*	F	0.90	1.30
	Pro	483	.	A	B	.	.	.	1.17	-0.74	.	*	.	0.60	0.76
	Val	484	.	A	B	.	.	.	0.31	-0.74	.	*	.	0.60	0.76
	Glu	485	A	A	0.10	-0.06	.	*	.	0.30	0.76
	Ala	486	.	A	B	.	.	.	-0.23	-0.31	.	*	.	0.30	0.76
	Lys	487	A	A	-0.12	0.17	.	*	.	-0.15	1.08
50	Leu	488	.	A	0.13	0.31	.	*	.	-0.10	0.54
	Pro	489	.	A	.	.	T	.	0.99	0.31	.	*	.	0.25	1.06
	Trp	490	.	A	.	.	T	.	0.40	0.21	.	*	.	0.10	0.92
	Phe	491	A	A	0.99	0.71	.	.	.	-0.45	1.13
	Lys	492	A	A	0.94	0.43	.	.	F	-0.30	1.26
55	Gln	493	.	A	0.94	0.00	*	.	F	0.80	2.08
	Ala	494	.	A	1.16	-0.23	*	.	F	0.80	1.98
	Gln	495	.	A	1.44	-1.01	*	.	F	1.10	1.72
	Glu	496	.	A	1.80	-1.01	*	.	F	1.10	1.72
60	Leu	497	A	A	1.17	-0.99	*	.	F	0.90	1.68
	Glu	498	A	A	0.58	-0.99	.	.	F	0.75	0.98
	Glu	499	A	A	0.31	-0.89	.	.	F	0.75	0.57
	Gly	500	A	A	0.01	-0.24	.	.	F	0.45	0.52
	Ala	501	A	A	0.01	-0.54	.	.	.	0.60	0.40

	Ala	502	A	A	0.82	-0.54	.	.	.	0.60	0.40
	Val	503	A	A	0.61	-0.54	.	.	.	0.85	0.70
	Ser	504	A	A	0.31	-0.54	.	.	F	1.40	1.07
5	Glu	505	.	A	B	.	.	.	-0.04	-0.66	.	.	F	1.65	1.42
	Glu	506	.	.	B	.	.	T	-0.34	-0.37	.	.	F	2.00	1.65
	Pro	507	T	T	0.03	-0.33	*	.	F	2.50	0.86
	Ser	508	T	T	0.93	-0.29	*	.	F	2.25	0.77
	Phe	509	.	.	B	.	.	T	0.64	-0.29	*	.	.	1.45	0.89
10	Ile	510	.	.	B	.	.	.	0.36	0.21	*	.	.	0.40	0.58
	Pro	511	T	.	0.06	0.70	*	.	.	0.25	0.46
	Lys	512	T	.	-0.32	0.70	*	.	.	0.00	0.71
	Ala	513	T	.	-0.69	0.41	*	.	.	0.15	1.02
	Trp	514	T	.	-0.30	0.30	.	.	.	0.30	0.35
15	Ser	515	.	.	B	.	.	T	-0.27	0.36	.	.	.	0.10	0.26
	Ala	516	.	.	B	.	.	T	-0.37	1.00	.	.	.	-0.20	0.19
	Cys	517	.	.	B	.	.	T	-1.08	0.99	.	.	.	-0.20	0.26
	Thr	518	.	.	B	.	.	T	-0.83	0.64	.	.	.	-0.20	0.10
	Val	519	.	.	B	B	.	.	-1.40	0.69	.	.	.	-0.60	0.10
20	Thr	520	.	.	B	B	.	.	-1.44	0.83	.	.	.	-0.60	0.14
	Cys	521	.	.	B	B	.	.	-1.17	0.69	.	.	.	-0.60	0.10
	Gly	522	.	.	.	B	T	.	-0.50	0.69	.	*	.	-0.20	0.19
	Val	523	.	.	B	B	.	.	-1.04	0.44	*	*	.	-0.60	0.22
	Gly	524	.	.	B	B	.	.	-0.08	0.60	*	*	F	-0.45	0.31
25	Thr	525	.	.	B	B	.	.	-0.66	0.03	*	*	F	-0.15	0.61
	Gln	526	.	.	B	B	.	.	-0.84	0.29	*	*	F	-0.15	0.58
	Val	527	.	.	B	B	.	.	-0.39	0.29	*	*	.	-0.30	0.43
	Arg	528	.	.	B	B	.	.	-0.20	-0.14	*	*	.	0.30	0.59
	Ile	529	.	.	B	B	.	.	0.14	-0.06	*	*	.	0.30	0.18
30	Val	530	.	.	B	B	.	.	-0.40	-0.06	*	*	.	0.30	0.42
	Arg	531	.	.	B	B	.	.	-1.21	-0.06	*	*	.	0.30	0.16
	Cys	532	.	.	B	B	.	.	-1.17	0.63	*	*	.	-0.60	0.19
	Gln	533	.	.	B	B	.	.	-1.58	0.63	*	*	.	-0.60	0.21
	Val	534	.	.	B	B	.	.	-1.39	0.37	.	*	.	-0.30	0.14
35	Leu	535	.	.	B	B	.	.	-0.83	1.16	.	*	.	-0.60	0.23
	Leu	536	.	.	B	B	.	.	-0.94	0.97	.	*	.	-0.60	0.18
	Ser	537	.	.	B	B	.	.	-0.58	0.97	*	*	.	-0.60	0.42
	Phe	538	.	.	B	B	.	.	-1.43	0.71	*	*	.	-0.60	0.68
	Ser	539	.	.	B	B	.	.	-1.17	0.67	*	.	F	-0.45	0.61
40	Gln	540	.	.	B	B	.	.	-0.36	0.49	*	.	F	-0.45	0.46
	Ser	541	.	.	B	B	.	.	-0.36	0.10	*	.	F	-0.15	0.89
	Val	542	.	.	B	B	.	.	-0.27	0.00	*	*	.	0.30	0.55
	Ala	543	.	.	B	B	.	.	-0.46	0.04	*	*	.	-0.30	0.49
	Asp	544	.	.	B	B	.	.	-0.16	0.33	.	*	.	-0.30	0.26
45	Leu	545	.	.	B	B	.	.	-0.16	-0.06	*	*	.	0.30	0.58
	Pro	546	.	.	B	.	.	.	-0.52	-0.70	*	.	.	0.80	0.99
	Ile	547	.	.	B	.	.	.	0.33	-0.63	.	.	.	0.80	0.32
	Asp	548	.	.	B	.	.	.	0.58	-0.63	.	*	F	0.95	0.67
	Glu	549	.	.	B	.	.	.	0.37	-0.89	.	.	F	1.29	0.43
50	Cys	550	T	.	1.22	-0.89	.	.	F	2.03	0.94
	Glu	551	T	.	1.22	-1.57	.	.	F	2.52	1.13
	Gly	552	T	1.52	-1.14	.	.	F	2.86	1.01
	Pro	553	T	T	1.22	-0.64	.	.	F	3.40	1.90
	Lys	554	T	1.22	-0.83	.	.	F	2.86	1.47
55	Pro	555	T	T	2.00	-0.43	*	.	F	2.42	2.57
	Ala	556	.	A	.	.	T	.	1.41	-0.86	*	.	F	1.98	3.26
	Ser	557	.	A	B	.	.	.	1.09	-0.79	.	.	F	1.24	1.64
	Gln	558	.	A	B	.	.	.	1.06	-0.21	*	.	F	0.45	0.57
	Arg	559	.	A	B	.	.	.	0.42	0.11	*	.	F	-0.15	0.88
60	Ala	560	.	.	B	.	.	.	0.29	0.11	.	.	.	-0.10	0.67
	Cys	561	.	.	B	.	.	.	0.67	0.16	.	*	.	-0.10	0.38
	Tyr	562	.	.	B	.	.	.	0.30	0.19	.	.	.	-0.10	0.30
	Ala	563	.	.	B	.	T	.	0.00	0.76	*	.	.	0.00	0.16
	Gly	564	T	-0.46	0.64	*	*	.	0.00	0.40

600

	Pro	565	T	T	.	0.13	0.50	.	*	F	0.35	0.25
	Cys	566	T	T	.	-0.09	-0.26	.	*	F	1.25	0.43
	Ser	567	T	T	.	-0.06	-0.07	.	.	F	1.25	0.31
5	Gly	568	.	.	B	0.53	-0.07	.	.	F	0.65	0.31
	Glu	569	.	.	B	0.18	-0.50	.	.	F	0.65	0.99
	Ile	570	.	.	B	0.39	-0.29	.	.	F	0.95	0.64
	Pro	571	.	.	B	0.84	-0.27	.	*	F	1.40	1.04
	Glu	572	T	.	.	1.14	-0.27	.	.	F	1.95	0.93
10	Phe	573	C	1.49	-0.27	.	.	F	2.20	2.21
	Asn	574	T	C	1.18	-0.96	.	.	F	3.00	2.47
	Pro	575	T	C	2.07	-0.90	.	.	F	2.70	2.06
	Asp	576	T	T	.	1.93	-0.90	.	.	F	2.85	3.97
	Glu	577	T	T	.	1.12	-1.26	.	*	F	2.80	2.45
15	Thr	578	T	T	.	1.12	-0.97	.	.	F	2.75	1.30
	Asp	579	T	T	.	0.78	-0.61	.	.	F	2.55	0.68
	Gly	580	T	T	.	0.64	-0.19	.	.	F	2.50	0.39
	Leu	581	.	.	B	.	.	T	.	-0.17	0.24	*	.	.	1.10	0.26
	Phe	582	.	.	B	-0.17	0.44	*	.	.	0.35	0.13
20	Gly	583	C	0.14	0.84	*	.	.	0.30	0.23
	Gly	584	.	A	C	-0.56	0.41	*	.	F	0.00	0.46
	Leu	585	.	A	C	-0.21	0.51	*	.	F	-0.25	0.46
	Gln	586	.	A	C	0.60	-0.27	*	.	F	0.65	0.78
	Asp	587	.	A	B	0.49	-0.70	*	.	F	0.90	1.37
25	Phe	588	.	A	B	0.59	-0.44	*	.	F	0.60	1.37
	Asp	589	.	A	B	0.93	-0.37	*	.	F	0.60	1.24
	Glu	590	.	A	B	1.46	-0.77	*	.	F	0.90	1.24
	Leu	591	.	A	C	1.46	0.14	*	*	.	0.05	1.50
	Tyr	592	.	A	C	1.21	-0.64	*	*	.	0.95	1.56
30	Asp	593	.	A	.	.	T	.	.	1.91	0.11	*	*	.	0.25	1.41
	Trp	594	.	A	.	.	T	.	.	1.57	0.11	*	.	.	0.25	2.96
	Glu	595	A	A	0.87	-0.14	*	.	.	0.45	1.87
	Tyr	596	T	.	.	1.37	-0.11	*	*	.	0.90	0.97
	Glu	597	T	.	.	1.66	0.37	*	*	.	0.45	1.33
35	Gly	598	T	.	.	0.99	-0.54	.	*	F	1.50	1.54
	Phe	599	T	.	.	0.98	0.03	.	*	F	0.76	0.53
	Thr	600	T	T	.	0.98	-0.34	*	.	F	1.87	0.41
	Lys	601	T	T	.	0.92	-0.34	*	.	F	2.18	0.71
	Cys	602	T	T	.	0.26	-0.39	*	.	F	2.64	1.10
40	Ser	603	T	T	.	0.26	-0.60	*	.	F	3.10	0.41
	Glu	604	T	.	.	0.61	-0.66	*	.	F	2.59	0.20
	Ser	605	T	.	.	0.58	-0.23	*	.	F	1.98	0.37
	Cys	606	T	T	.	-0.32	-0.37	*	.	F	2.00	0.28
	Gly	607	T	T	.	0.34	-0.11	.	.	F	1.82	0.12
45	Gly	608	T	T	.	0.64	0.29	*	.	F	1.04	0.15
	Gly	609	T	C	0.06	-0.10	*	.	F	1.57	0.49
	Val	610	.	.	B	-0.50	-0.17	.	.	F	1.30	0.50
	Gln	611	.	.	B	-0.69	0.04	.	.	F	0.57	0.38
	Glu	612	.	.	B	-0.64	0.26	.	.	.	0.29	0.28
50	Ala	613	.	.	B	B	.	.	.	-0.97	0.21	.	.	.	-0.04	0.51
	Val	614	.	.	B	B	.	.	.	-1.43	0.14	*	.	.	-0.17	0.16
	Val	615	.	.	B	B	.	.	.	-0.58	0.43	*	.	.	-0.60	0.08
	Ser	616	.	.	B	-0.53	0.83	*	.	.	-0.40	0.12
	Cys	617	.	.	B	-0.53	0.33	*	.	.	0.16	0.32
55	Leu	618	-0.26	0.09	*	*	.	0.82	0.76
	Asn	619	T	.	.	0.71	-0.07	*	.	F	1.83	0.81
	Lys	620	T	.	.	1.57	-0.46	*	.	F	2.24	2.98
	Gln	621	C	1.66	-1.03	*	.	F	2.60	6.25
	Thr	622	C	1.73	-1.29	*	*	F	2.34	6.01
60	Arg	623	.	A	C	2.54	-1.19	*	*	F	1.88	3.04
	Glu	624	.	A	C	2.54	-1.19	*	*	F	1.62	3.04
	Pro	625	.	A	C	2.50	-1.59	*	*	F	1.36	3.64
	Ala	626	.	A	.	.	T	.	.	1.69	-1.67	.	*	F	1.30	2.99
	Glu	627	.	A	.	.	T	.	.	1.33	-0.99	.	*	F	1.30	1.42

601

5	Glu	628	A	A	0.37	-0.41	.	*	F	0.45	0.49
	Asn	629	.	A	B	B	.	.	0.06	-0.20	.	.	F	0.45	0.36
	Leu	630	.	A	B	B	.	.	-0.03	-0.21	*	*	.	0.58	0.30
	Cys	631	.	A	B	B	.	.	0.67	0.17	*	*	.	0.26	0.23
	Val	632	.	A	B	B	.	.	0.78	0.17	*	*	.	0.54	0.28
	Thr	633	.	.	B	.	.	T	0.57	-0.23	*	.	F	1.97	0.68
	Ser	634	T	T	0.36	-0.49	*	*	F	2.80	1.95
	Arg	635	T	T	1.17	-0.63	*	.	F	2.82	4.07
10	Arg	636	.	.	B	.	.	T	1.02	-0.87	*	.	F	2.14	4.88
	Pro	637	T	1.07	-0.67	*	.	F	2.06	3.00
	Pro	638	T	T	1.42	-0.37	*	.	F	1.68	1.26
	Gln	639	T	T	1.42	-0.37	*	.	F	1.40	1.29
	Leu	640	.	.	B	.	.	T	0.64	0.01	*	.	F	0.40	1.12
15	Leu	641	.	.	B	.	.	T	0.53	0.16	*	*	F	0.49	0.39
	Lys	642	.	.	B	.	.	T	-0.07	0.13	.	.	F	0.73	0.36
	Ser	643	.	.	B	.	.	T	0.14	0.41	.	.	F	0.67	0.36
	Cys	644	T	T	-0.07	-0.27	.	.	.	2.06	0.73
	Asn	645	T	.	0.08	-0.53	.	.	.	2.40	0.56
20	Leu	646	T	.	0.68	0.04	.	.	F	1.41	0.23
	Asp	647	T	0.04	0.09	*	.	F	1.17	0.65
	Pro	648	T	T	0.46	0.01	*	*	F	1.13	0.41
	Cys	649	T	0.83	-0.39	*	*	F	1.29	0.97
	Pro	650	.	.	B	.	.	T	0.83	-0.16	.	*	.	0.70	0.61
25	Ala	651	.	A	B	.	.	.	0.76	-0.16	.	*	.	0.30	0.68
	Arg	652	.	A	B	.	.	.	0.41	0.10	.	*	.	-0.30	0.90
	Trp	653	.	A	B	.	.	.	0.67	-0.04	.	*	.	0.30	0.57
	Glu	654	.	A	B	.	.	.	1.04	-0.47	.	*	.	0.45	1.13
	Ile	655	.	A	.	.	T	.	0.96	-0.06	.	*	.	0.70	0.61
30	Gly	656	.	A	.	.	T	.	1.33	0.33	.	*	F	0.38	0.78
	Lys	657	T	.	0.56	-0.16	.	*	F	1.31	0.69
	Trp	658	T	.	0.54	0.41	*	.	F	0.54	0.53
	Ser	659	T	-0.27	0.11	*	.	F	0.97	0.72
	Pro	660	T	T	0.31	0.37	*	.	F	1.30	0.30
35	Cys	661	T	T	-0.01	0.86	.	.	.	0.72	0.41
	Ser	662	T	T	-0.40	0.51	.	.	.	0.59	0.16
	Leu	663	.	.	B	B	.	.	-0.97	0.56	.	.	.	-0.34	0.10
	Thr	664	.	.	B	B	.	.	-1.01	0.77	.	.	.	-0.47	0.14
	Cys	665	.	.	B	B	.	.	-1.61	0.63	.	*	.	-0.60	0.11
40	Gly	666	.	.	B	B	.	.	-0.94	0.93	.	*	.	-0.60	0.11
	Val	667	.	.	B	B	.	.	-0.96	0.64	.	*	.	-0.60	0.13
	Gly	668	.	.	B	B	.	.	-0.03	0.64	.	*	.	-0.60	0.34
	Leu	669	.	.	B	B	.	.	0.28	0.07	.	*	.	-0.30	0.68
	Gln	670	.	.	B	B	.	.	0.09	-0.36	.	*	F	0.60	1.53
45	Thr	671	.	.	B	B	.	.	-0.27	-0.36	.	*	F	0.60	1.15
	Arg	672	.	.	B	B	.	.	-0.08	0.00	*	*	F	0.00	1.20
	Asp	673	.	.	B	B	.	.	-0.03	-0.11	.	*	F	0.45	0.37
	Val	674	.	.	B	B	.	.	0.74	-0.13	.	*	.	0.30	0.35
	Phe	675	.	.	B	B	.	.	-0.07	-0.11	.	.	.	0.30	0.24
50	Cys	676	.	.	B	.	.	T	-0.57	0.57	.	.	.	-0.20	0.12
	Ser	677	.	.	B	.	.	T	-0.98	1.26	.	.	.	-0.20	0.13
	His	678	.	.	B	.	.	T	-0.87	1.00	.	.	.	-0.20	0.20
	Leu	679	T	-0.01	0.21	.	.	.	0.30	0.75
	Leu	680	.	A	0.09	-0.36	*	.	.	0.50	0.96
55	Ser	681	.	A	0.76	-0.13	*	.	F	0.65	0.70
	Arg	682	.	A	1.06	-0.23	*	.	F	0.80	1.37
	Glu	683	.	A	0.78	-0.91	*	.	F	1.10	2.87
	Met	684	.	A	.	.	T	.	0.73	-1.11	*	.	F	1.30	3.09
	Asn	685	.	A	0.66	-0.86	*	.	F	1.10	1.17
60	Glu	686	.	A	B	.	.	.	0.14	-0.17	*	.	F	0.45	0.47
	Thr	687	.	A	B	.	.	.	-0.56	0.51	*	.	.	-0.60	0.40
	Val	688	.	A	B	.	.	.	-0.56	0.40	.	.	.	-0.60	0.25
	Ile	689	.	A	B	.	.	.	0.04	0.00	.	.	.	-0.30	0.24
	Leu	690	.	A	B	.	.	.	-0.77	0.00	.	.	.	-0.30	0.29

	Ala	691	A	A	-1.43	0.20	*	.	-0.30	0.32
	Asp	692	A	A	-1.01	0.13	*	.	-0.30	0.24
	Glu	693	.	A	B	.	.	.	-0.16	-0.56	*	.	0.60	0.58
5	Leu	694	.	A	B	.	.	.	0.52	-0.84	*	.	0.60	0.99
	Cys	695	.	A	.	.	T	.	1.38	-0.91	*	.	F 1.45	0.92
	Arg	696	.	A	.	.	T	.	1.76	-0.91	*	.	F 1.90	1.06
	Gln	697	.	A	.	.	.	C	1.46	-0.49	*	.	F 1.70	1.99
	Pro	698	.	A	.	.	T	.	1.14	-0.79	*	.	F 2.50	4.98
	Lys	699	T	C	1.10	-0.87	*	.	F 3.00	3.67
10	Pro	700	T	T	1.77	-0.23	.	.	F 2.60	1.57
	Ser	701	T	T	1.07	-0.23	.	.	F 2.30	1.76
	Thr	702	.	.	B	.	.	T	0.40	-0.16	.	.	F 1.45	0.89
	Val	703	.	.	B	B	.	.	0.61	0.41	.	*	-0.30	0.31
	Gln	704	.	.	B	B	.	.	0.68	0.39	*	*	-0.30	0.37
15	Ala	705	.	.	B	B	.	.	0.19	0.00	*	*	-0.30	0.50
	Cys	706	.	.	B	.	.	.	0.49	0.30	*	*	-0.10	0.59
	Asn	707	T	T	0.13	0.06	*	*	0.50	0.54
	Arg	708	T	T	0.78	0.23	*	*	0.50	0.29
	Phe	709	T	T	0.57	0.16	*	*	0.50	0.83
20	Asn	710	T	T	0.57	0.01	.	*	0.50	0.80
	Cys	711	C	0.94	0.11	.	*	0.10	0.41
	Pro	712	C	0.70	1.03	.	*	0.00	0.50
	Pro	713	T	T	0.38	1.00	.	*	0.20	0.49
	Ala	714	T	T	0.49	1.03	.	.	0.35	1.41
25	Trp	715	T	T	0.49	0.96	.	.	0.20	0.92
	Tyr	716	.	.	B	.	.	T	0.87	0.93	.	*	-0.05	1.03
	Pro	717	T	T	1.08	1.41	.	*	0.35	1.07
	Ala	718	T	T	1.08	1.31	.	*	0.35	1.77
	Gln	719	T	T	1.00	0.83	.	.	0.35	1.75
30	Trp	720	T	.	0.99	0.64	*	*	0.00	0.61
	Gln	721	.	.	B	.	.	T	1.34	0.60	*	*	0.00	0.80
	Pro	722	T	T	1.24	0.10	*	*	F 0.65	0.91
	Cys	723	T	T	1.17	0.19	*	*	F 1.05	1.25
	Ser	724	T	T	0.82	-0.16	*	*	F 1.75	0.39
35	Arg	725	T	.	0.77	-0.13	*	*	F 1.80	0.25
	Thr	726	T	.	0.42	-0.13	*	.	F 2.05	0.46
	Cys	727	T	T	-0.22	-0.27	*	.	F 2.50	0.34
	Gly	728	T	T	0.44	-0.01	*	.	F 2.25	0.13
	Gly	729	T	T	0.79	0.39	.	*	F 1.40	0.15
40	Gly	730	T	0.79	-0.10	.	.	F 1.55	0.57
	Val	731	.	A	.	.	.	C	1.10	-0.67	.	.	F 1.35	1.13
	Gln	732	.	A	B	.	.	.	0.91	-1.10	.	.	F 0.90	1.98
	Lys	733	.	A	B	.	.	.	0.44	-0.89	.	.	F 0.90	1.48
45	Arg	734	.	A	B	.	.	.	0.12	-0.63	.	.	F 0.90	1.65
	Glu	735	.	A	B	.	.	.	0.51	-0.70	.	.	0.60	0.51
	Val	736	.	A	B	.	.	.	1.37	-1.10	.	*	0.60	0.51
	Leu	737	.	A	B	.	.	.	1.48	-0.70	.	*	0.60	0.45
	Cys	738	.	A	B	.	.	.	0.83	-0.70	*	*	0.60	0.51
50	Lys	739	.	A	B	.	.	.	0.13	-0.09	*	.	F 0.45	0.68
	Gln	740	.	A	B	.	.	.	0.13	-0.23	.	*	F 0.70	0.83
	Arg	741	.	A	B	.	.	.	0.64	-0.91	.	.	F 1.40	2.60
	Met	742	.	A	B	.	.	.	1.16	-1.06	.	.	F 1.65	1.28
	Ala	743	.	.	B	.	.	T	1.12	-0.67	.	.	F 2.15	0.99
55	Asp	744	T	T	0.27	-0.29	.	.	F 2.50	0.44
	Gly	745	T	0.27	0.40	*	.	F 1.15	0.37
	Ser	746	T	-0.66	-0.21	*	.	F 1.80	0.63
	Phe	747	.	A	B	.	.	.	-0.27	-0.03	.	.	0.80	0.31
	Leu	748	.	A	B	.	.	.	0.32	0.40	.	.	-0.35	0.48
	Glu	749	.	A	B	.	.	.	0.01	-0.03	*	.	0.30	0.63
60	Leu	750	.	A	B	.	.	.	-0.34	0.07	*	.	-0.15	1.04
	Pro	751	.	A	.	.	T	.	-0.71	0.07	*	.	F 0.40	1.10
	Glu	752	.	A	.	.	T	.	-0.31	-0.04	*	.	F 0.85	0.34
	Thr	753	.	A	.	.	T	.	-0.09	0.34	*	.	F 0.25	0.55

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5	Phe	754	.	A	.	.	T	.	.	-0.39	0.16	*	.	.	0.10	0.36
	Cys	755	.	A	.	.	T	.	.	0.47	0.11	*	.	.	0.10	0.28
	Ser	756	T	T	.	0.47	0.11	*	.	.	0.50	0.39
	Ala	757	T	T	.	-0.12	0.06	*	.	F	0.65	0.69
	Ser	758	T	T	.	-0.48	-0.23	*	.	F	1.40	1.30
10	Lys	759	T	C	0.22	-0.23	*	.	F	1.05	0.52
	Pro	760	T	T	.	0.89	-0.21	*	.	F	1.25	0.89
	Ala	761	T	T	.	0.60	-0.31	*	.	.	1.25	1.15
	Cys	762	.	.	B	.	.	T	.	0.52	-0.20	*	.	.	1.01	0.58
	Gln	763	.	.	B	.	.	T	.	0.87	0.37	*	.	.	0.72	0.20
15	Gln	764	.	.	B	0.87	-0.06	.	.	.	1.43	0.40
	Ala	765	.	.	B	1.08	-0.56	*	.	.	2.19	1.49
	Cys	766	T	T	.	1.67	-1.13	.	.	.	3.10	1.44
	Lys	767	T	T	.	1.67	-1.53	.	.	F	2.94	1.38
	Lys	768	T	T	.	1.46	-1.36	.	.	F	2.48	0.73
20	Asp	769	T	T	.	1.16	-1.43	.	.	F	2.57	2.12
	Asp	770	T	.	.	1.74	-1.61	.	.	F	2.31	1.42
	Cys	771	.	.	B	.	.	T	.	2.12	-1.61	.	.	F	2.05	1.23
	Pro	772	.	.	B	.	.	T	.	1.27	-0.70	.	.	F	2.15	0.77
	Ser	773	.	.	B	.	T	T	.	0.41	-0.01	.	.	F	2.50	0.38
25	Glu	774	.	.	B	.	.	T	.	0.11	0.67	.	.	F	0.95	0.59
	Trp	775	.	.	B	0.11	0.49	.	.	.	0.35	0.51
	Leu	776	.	.	B	0.49	0.06	.	.	.	0.40	0.64
	Leu	777	T	T	.	0.39	0.59	.	.	.	0.45	0.39
	Ser	778	T	T	.	0.69	1.07	*	.	F	0.35	0.53
30	Asp	779	T	T	.	0.02	0.16	*	.	F	0.80	1.11
	Trp	780	T	T	.	0.01	0.04	.	.	F	0.65	0.72
	Thr	781	T	.	.	0.51	-0.26	*	.	F	1.30	0.72
	Glu	782	T	.	.	1.02	-0.16	*	.	F	1.55	0.62
	Cys	783	T	.	.	0.66	0.23	.	.	F	1.20	0.80
35	Ser	784	T	.	.	0.31	-0.11	*	.	F	2.05	0.30
	Thr	785	T	T	.	0.60	-0.17	.	.	F	2.50	0.17
	Ser	786	T	T	.	0.57	-0.17	.	.	F	2.25	0.55
	Cys	787	T	T	.	0.26	-0.31	.	.	F	2.30	0.40
	Gly	788	T	T	.	0.92	-0.21	.	.	F	2.35	0.40
40	Glu	789	T	.	.	0.91	-0.30	.	.	F	2.20	0.52
	Gly	790	T	.	.	1.33	-0.20	.	.	F	2.40	1.40
	Thr	791	T	.	.	1.33	-0.77	.	.	F	3.00	2.78
	Gln	792	.	.	B	.	.	T	.	1.41	-0.81	.	*	F	2.50	2.15
	Thr	793	.	.	B	.	.	T	.	0.87	-0.31	.	.	F	1.90	2.19
45	Arg	794	.	.	B	.	.	T	.	0.20	-0.06	*	.	F	1.60	1.06
	Ser	795	.	.	B	.	.	T	.	0.66	0.03	.	.	F	0.55	0.33
	Ala	796	.	A	B	1.01	-0.37	.	*	.	0.30	0.45
	Ile	797	.	A	B	0.41	-0.86	.	*	.	0.60	0.46
	Cys	798	.	A	B	-0.09	-0.24	.	*	.	0.30	0.34
50	Arg	799	.	A	B	-0.16	0.06	.	*	.	-0.30	0.28
	Lys	800	.	A	B	-0.17	-0.44	*	.	.	0.30	0.79
	Met	801	.	A	B	0.08	-0.64	*	.	.	0.75	2.12
	Leu	802	.	A	B	0.16	-0.79	*	.	F	0.90	1.07
	Lys	803	.	.	B	.	.	T	.	0.52	-0.10	*	*	F	0.85	0.44
55	Thr	804	.	.	B	.	.	T	.	0.10	0.29	*	*	F	0.25	0.60
	Gly	805	.	.	B	.	.	T	.	-0.80	0.16	*	.	F	0.40	1.04
	Leu	806	.	.	B	.	.	T	.	-1.06	0.11	*	*	F	0.25	0.39
	Ser	807	.	.	B	B	.	.	.	-0.24	0.76	*	*	F	-0.45	0.20
	Thr	808	.	.	B	B	.	.	.	-0.59	0.67	*	.	.	-0.60	0.32
60	Val	809	.	.	B	B	.	.	.	-0.59	0.63	*	.	.	-0.60	0.53
	Val	810	.	.	B	B	.	.	.	-1.06	0.43	*	.	F	-0.45	0.57
	Asn	811	.	.	B	.	.	T	.	-0.91	0.73	*	.	F	-0.05	0.32
	Ser	812	.	.	B	.	.	T	.	-0.82	0.81	.	.	F	-0.05	0.23
	Thr	813	.	.	B	.	.	T	.	-0.72	0.60	.	.	F	-0.05	0.49
60	Leu	814	.	.	B	.	.	T	.	-0.68	0.39	.	.	F	0.25	0.47
	Cys	815	.	.	B	-0.03	0.67	.	*	F	-0.25	0.29
	Pro	816	.	.	B	-0.73	0.71	.	*	F	-0.25	0.31

	Pro	817	.	.	B	.	.	.	-0.73	1.01	.	.	F	-0.25	0.32
	Leu	818	.	.	B	.	.	T	-0.72	0.71	.	*	.	-0.20	0.81
	Pro	819	T	T	-0.21	0.53	.	*	.	0.20	0.70
	Phe	820	T	T	-0.43	0.49	*	*	F	0.35	0.61
5	Ser	821	.	.	B	.	.	T	-0.11	0.74	*	*	F	-0.05	0.52
	Ser	822	.	.	.	B	T	.	-0.11	0.06	*	*	F	0.25	0.66
	Ser	823	.	.	.	B	T	.	0.03	0.06	*	*	F	0.40	1.17
	Ile	824	.	.	B	B	.	.	-0.36	-0.16	*	*	F	0.45	0.47
10	Arg	825	.	.	B	.	.	T	-0.47	0.07	*	*	F	0.25	0.35
	Pro	826	T	T	-0.76	0.37	.	*	.	0.50	0.21
	Cys	827	T	T	-0.77	0.49	.	*	.	0.20	0.31
	Met	828	.	.	B	.	.	T	-1.13	0.29	.	*	.	0.10	0.23
	Leu	829	.	.	B	.	.	.	-0.83	0.86	.	*	.	-0.40	0.08
	Ala	830	.	.	B	.	.	.	-0.83	0.93	.	*	.	-0.40	0.15
15	Thr	831	.	.	B	.	.	.	-0.83	0.36	*	.	.	0.24	0.29
	Cys	832	.	.	B	.	.	.	-0.51	0.17	*	.	.	0.58	0.55
	Ala	833	.	.	B	.	.	.	0.20	-0.09	*	.	.	1.52	0.54
	Arg	834	.	.	B	.	.	T	0.80	-0.59	*	.	F	2.51	0.73
20	Pro	835	T	T	1.09	-0.64	*	.	F	3.40	2.10
	Gly	836	T	T	1.09	-0.83	*	*	F	3.06	2.79
	Arg	837	T	1.80	-0.84	*	.	F	2.80	2.05
	Pro	838	T	T	2.36	-0.84	*	*	F	2.94	2.66
	Ser	839	T	T	1.94	-0.77	*	*	F	2.88	3.65
25	Thr	840	T	T	1.94	-0.81	*	*	F	2.82	2.50
	Lys	841	T	T	2.26	-0.39	*	*	F	2.80	2.50
	His	842	1.26	-0.31	*	*	F	2.12	2.54
	Ser	843	T	0.88	-0.01	.	*	F	2.04	1.23
	Pro	844	.	.	B	.	.	T	0.59	0.00	.	.	F	0.81	0.62
30	His	845	.	.	B	.	.	T	0.31	0.50	.	*	.	0.08	0.46
	Ile	846	.	.	B	.	.	T	0.38	0.50	.	.	.	-0.20	0.35
	Ala	847	A	A	0.46	0.11	*	.	.	-0.30	0.44
	Ala	848	A	A	-0.10	-0.31	*	.	.	0.30	0.65
	Ala	849	.	A	B	B	.	.	-0.13	-0.17	.	.	.	0.30	0.69
35	Arg	850	.	A	B	B	.	.	-0.99	-0.10	.	.	.	0.45	1.07
	Lys	851	.	A	B	B	.	.	-0.10	0.09	.	.	.	-0.30	0.74
	Val	852	.	A	B	B	.	.	0.18	-0.01	*	*	.	0.45	1.27
	Tyr	853	.	A	B	B	.	.	0.88	-0.03	*	.	.	0.30	0.93
	Ile	854	.	.	B	B	.	.	1.58	-0.03	*	*	.	0.30	0.91
40	Gln	855	.	.	B	B	.	.	1.47	-0.03	*	.	.	0.45	2.41
	Thr	856	.	.	B	B	.	.	1.53	-0.27	*	*	F	0.60	2.67
	Arg	857	.	A	B	B	.	.	2.43	-1.03	*	*	F	0.90	7.46
	Arg	858	.	A	B	B	.	.	1.87	-1.71	.	.	F	0.90	8.61
	Gln	859	.	A	.	B	T	.	2.72	-1.43	.	*	F	1.30	4.92
45	Arg	860	.	A	.	B	T	.	2.02	-1.41	.	.	F	1.30	3.42
	Lys	861	.	A	B	.	.	.	1.48	-0.63	*	.	F	0.90	1.51
	Leu	862	.	.	B	B	.	.	0.51	0.01	*	.	.	-0.30	0.65
	His	863	.	.	B	B	.	.	0.06	0.26	.	.	.	-0.30	0.25
	Phe	864	.	.	B	B	.	.	-0.29	0.69	*	.	.	-0.60	0.12
50	Val	865	.	.	B	B	.	.	-1.10	1.11	*	.	.	-0.60	0.15
	Val	866	.	.	B	B	.	.	-1.73	1.21	.	*	.	-0.60	0.09
	Gly	867	.	.	B	B	.	.	-1.17	1.21	.	.	.	-0.60	0.11
	Gly	868	.	.	B	B	.	.	-1.94	1.19	.	.	.	-0.60	0.23
	Phe	869	.	.	B	B	.	.	-2.06	1.23	.	.	.	-0.60	0.25
55	Ala	870	.	.	B	B	.	.	-1.41	1.27	*	.	.	-0.60	0.21
	Tyr	871	.	.	B	B	.	.	-0.51	1.27	*	.	.	-0.60	0.33
	Leu	872	.	.	B	B	.	.	-0.48	0.84	*	.	.	-0.60	0.76
	Leu	873	.	.	B	.	.	T	-0.72	0.54	.	.	.	-0.05	1.09
	Pro	874	.	.	B	.	.	T	-0.88	0.54	.	.	F	-0.05	0.70
60	Lys	875	T	T	-1.14	0.43	.	.	F	0.35	0.63
	Thr	876	.	.	B	.	.	T	-1.71	0.39	*	*	F	0.25	0.57
	Ala	877	.	.	B	B	.	.	-0.79	0.39	*	*	.	-0.30	0.30
	Val	878	.	.	B	B	.	.	-0.64	-0.04	.	*	.	0.30	0.30
	Val	879	.	.	B	B	.	.	-0.64	0.53	.	*	.	-0.60	0.11

	Leu	880	.	.	B	B	.	.	.	-1.28	0.47	*	*	.	-0.32	0.17
	Arg	881	.	.	B	B	.	.	.	-0.86	0.47	*	*	.	-0.04	0.23
	Cys	882	.	.	B	.	.	T	.	-0.16	-0.17	*	*	.	1.54	0.61
5	Pro	883	.	.	B	.	.	T	.	-0.16	-0.81	*	*	.	2.27	1.44
	Ala	884	T	T	.	0.81	-0.86	*	*	.	2.80	0.55
	Arg	885	.	.	B	.	.	T	.	1.67	-0.86	*	*	F	2.42	2.00
	Arg	886	.	.	B	B	.	.	.	1.34	-1.43	*	*	F	1.74	2.58
	Val	887	.	.	B	B	.	.	.	1.20	-1.43	*	.	F	1.46	3.95
10	Arg	888	.	.	B	B	.	.	.	0.52	-1.24	*	.	F	1.18	1.66
	Lys	889	.	.	B	0.80	-0.56	*	.	F	0.95	0.60
	Pro	890	.	.	B	0.40	-0.07	*	.	F	0.80	1.16
	Leu	891	.	A	B	0.29	0.20	*	*	.	-0.30	0.62
	Ile	892	.	A	B	1.19	0.20	*	.	.	0.04	0.54
15	Thr	893	.	A	B	1.08	0.20	*	.	.	0.38	0.70
	Trp	894	.	A	B	0.69	-0.23	*	*	.	1.47	1.41
	Glu	895	.	.	B	.	.	T	.	0.90	-0.49	*	.	F	2.36	1.99
	Lys	896	T	T	.	1.68	-0.77	*	.	F	3.40	2.39
	Asp	897	T	T	.	1.76	-0.76	*	*	F	3.06	3.09
20	Gly	898	T	T	.	1.18	-0.99	*	.	F	2.72	1.47
	Gln	899	.	.	.	B	T	.	.	1.17	-0.30	*	.	F	1.53	0.52
	His	900	.	.	.	B	.	.	C	0.87	0.09	*	.	.	0.24	0.41
	Leu	901	.	.	B	B	.	.	.	0.51	0.47	*	.	.	-0.60	0.56
	Ile	902	.	.	B	B	.	.	.	0.48	0.53	.	.	.	-0.60	0.47
25	Ser	903	.	.	B	B	.	.	.	-0.03	0.63	.	.	F	-0.45	0.47
	Ser	904	.	.	B	B	.	.	.	-0.34	0.77	.	.	F	-0.45	0.42
	Thr	905	.	.	B	B	.	.	.	-1.17	0.57	.	.	F	-0.45	0.87
	His	906	.	.	B	B	.	.	.	-0.94	0.53	.	.	.	-0.60	0.48
	Val	907	.	.	B	B	.	.	.	-0.27	0.64	.	.	.	-0.60	0.36
30	Thr	908	.	.	B	B	.	.	.	-0.67	0.69	.	.	.	-0.60	0.39
	Val	909	.	.	B	B	.	.	.	-0.71	0.99	.	.	.	-0.60	0.25
	Ala	910	.	.	B	.	.	T	.	-0.64	0.91	.	.	.	-0.20	0.33
	Pro	911	.	.	B	.	.	T	.	-1.42	1.03	.	.	.	-0.20	0.36
	Phe	912	T	T	.	-0.52	1.23	.	*	.	0.20	0.40
35	Gly	913	.	.	B	.	.	T	.	-1.10	0.59	.	*	.	-0.20	0.78
	Tyr	914	.	.	B	B	.	.	.	-0.28	0.77	*	.	.	-0.60	0.36
	Leu	915	.	.	B	B	.	.	.	0.42	0.84	*	.	.	-0.60	0.56
	Lys	916	.	.	B	B	.	.	.	-0.18	0.06	.	.	.	-0.15	1.11
	Ile	917	.	.	B	B	.	.	.	0.57	0.31	.	.	.	-0.30	0.58
40	His	918	.	.	B	B	.	.	.	0.70	-0.44	*	*	.	0.79	1.41
	Arg	919	.	.	B	B	.	.	.	0.64	-0.70	.	.	.	1.43	1.09
	Leu	920	.	.	B	B	.	.	.	1.46	-0.31	.	.	.	1.47	2.09
	Lys	921	.	.	B	.	.	T	.	0.82	-1.00	.	.	F	2.66	2.56
	Pro	922	T	T	.	1.37	-1.00	.	.	F	3.40	1.32
45	Ser	923	T	T	.	0.54	-0.57	.	*	F	3.06	1.59
	Asp	924	T	T	.	0.19	-0.61	.	*	F	2.57	0.59
	Ala	925	.	.	B	B	.	.	.	0.69	0.14	.	.	F	0.53	0.60
	Gly	926	.	.	B	B	.	.	.	-0.02	0.20	.	.	.	0.04	0.64
	Val	927	.	.	B	B	.	.	.	-0.11	0.39	.	.	.	-0.30	0.21
50	Tyr	928	.	.	B	B	.	.	.	-0.40	0.77	.	.	.	-0.60	0.27
	Thr	929	.	.	B	B	.	.	.	-0.74	0.77	.	.	.	-0.60	0.28
	Cys	930	.	.	B	B	.	.	.	-0.37	0.77	.	.	.	-0.30	0.37
	Ser	931	T	T	.	-0.61	0.56	*	.	.	0.80	0.37
	Ala	932	T	C	0.36	0.30	*	.	F	1.35	0.26
55	Gly	933	T	C	0.60	-0.19	.	.	F	2.25	0.94
	Pro	934	T	C	0.88	-0.76	.	*	F	3.00	1.21
	Ala	935	.	A	C	0.84	-0.64	.	.	F	2.30	1.64
	Arg	936	A	A	0.29	-0.36	.	*	F	1.50	1.43
	Glu	937	.	A	B	-0.01	-0.14	.	*	.	0.90	0.69
60	His	938	.	A	B	0.38	0.11	.	*	.	0.00	0.48
	Phe	939	.	A	B	-0.22	-0.39	.	*	.	0.30	0.49
	Val	940	.	A	B	-0.52	0.30	.	*	.	-0.30	0.23
	Ile	941	.	A	B	-0.98	0.99	.	*	.	-0.60	0.12
	Lys	942	.	A	B	-1.32	0.91	.	.	.	-0.35	0.14

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	Leu	943	.	A	B	.	.	.	-1.29	0.56	.	*	.	-0.10	0.18
	Ile	944	.	A	.	.	T	.	-0.48	0.31	*	*	.	0.85	0.42
	Gly	945	T	0.42	-0.37	*	.	F	2.05	0.41
5	Gly	946	T	T	0.50	-0.37	*	.	F	2.50	0.99
	Asn	947	T	-0.40	-0.37	*	.	F	2.20	1.17
	Arg	948	.	.	B	.	.	T	-0.18	-0.41	*	*	F	1.60	0.87
	Lys	949	.	.	B	B	.	.	0.82	-0.34	*	*	F	0.95	0.89
	Leu	950	.	.	B	B	.	.	0.96	-0.77	*	.	.	1.00	1.09
10	Val	951	.	.	B	B	.	.	0.49	-0.74	*	.	.	0.60	0.86
	Ala	952	.	.	B	B	.	.	0.19	-0.06	*	.	.	0.60	0.35
	Arg	953	.	.	B	.	.	.	-0.13	0.33	.	.	.	0.50	0.58
	Pro	954	.	.	B	.	.	.	-0.07	0.07	*	*	F	1.10	1.20
	Leu	955	0.44	-0.57	.	*	F	2.50	2.32
15	Ser	956	T	1.30	-0.69	*	.	F	3.00	1.59
	Pro	957	T	1.89	-0.69	*	*	F	2.70	1.78
	Arg	958	T	1.78	-1.11	*	*	F	2.40	3.74
	Ser	959	T	1.13	-1.80	*	*	F	2.10	4.83
	Glu	960	.	A	B	.	.	.	1.13	-1.54	.	*	F	1.20	2.32
20	Glu	961	.	A	B	.	.	.	0.84	-1.29	*	*	F	0.75	0.98
	Glu	962	.	A	B	.	.	.	0.71	-0.79	.	*	F	0.75	0.74
	Val	963	.	A	B	.	.	.	0.71	-0.74	.	*	.	0.60	0.42
	Leu	964	A	A	1.06	-0.74	.	.	.	0.94	0.48
	Ala	965	A	A	0.71	-0.74	.	.	.	1.28	0.55
25	Gly	966	T	.	0.37	-0.31	.	.	F	2.07	0.73
	Arg	967	T	T	0.16	-0.53	.	.	F	2.91	0.88
	Lys	968	T	T	1.06	-0.79	.	.	F	3.40	1.35
	Gly	969	T	1.87	-1.29	.	.	F	2.86	2.72
	Gly	970	T	1.87	-1.71	.	.	F	2.52	2.40
30	Pro	971	.	A	1.40	-1.21	.	.	F	1.78	1.21
	Lys	972	.	A	1.29	-0.53	.	.	F	1.44	1.01
	Glu	973	.	A	B	.	.	.	0.93	-0.56	*	*	F	0.90	1.77
	Ala	974	A	A	1.24	-0.50	*	.	F	0.60	1.65
	Leu	975	.	A	B	.	.	.	1.63	-0.43	*	.	F	0.60	1.12
35	Gln	976	.	A	B	.	.	.	1.81	-0.43	*	.	F	0.60	1.30
	Thr	977	.	A	B	.	.	.	1.77	0.07	.	.	F	0.28	1.75
	His	978	.	A	1.77	-0.03	.	.	F	1.36	3.67
	Lys	979	.	A	2.01	-0.31	.	.	F	1.64	3.41
	His	980	T	1.93	-0.29	.	.	F	2.32	2.34
40	Gln	981	T	T	1.23	-0.09	.	.	F	2.80	1.21
	Asn	982	T	T	1.24	0.20	.	.	F	1.77	0.52
	Gly	983	.	.	B	.	.	T	1.28	0.59	*	.	F	0.79	0.51
	Ile	984	.	.	B	.	.	.	0.89	0.49	*	.	.	0.16	0.48
	Phe	985	.	.	B	.	.	T	0.62	0.51	*	.	F	0.23	0.29
45	Ser	986	T	0.67	0.50	*	.	F	0.15	0.40
	Asn	987	T	0.08	0.07	*	.	F	0.60	1.13
	Gly	988	T	0.42	-0.11	*	.	F	1.20	1.32
	Ser	989	.	A	1.36	-0.90	*	*	F	1.10	1.71
	Lys	990	.	A	2.17	-1.29	*	*	F	1.10	2.13
50	Ala	991	.	A	2.12	-1.69	*	.	F	1.10	4.21
	Glu	992	.	A	B	.	.	.	1.31	-1.69	*	.	F	0.90	3.11
	Lys	993	.	A	B	.	.	.	1.07	-1.39	*	.	F	0.90	1.28
	Arg	994	.	A	B	.	.	.	0.78	-0.89	*	*	F	0.90	1.28
	Gly	995	.	A	B	.	.	.	0.73	-0.89	*	*	F	0.75	0.75
55	Leu	996	.	A	B	.	.	.	1.11	-0.49	.	.	.	0.30	0.60
	Ala	997	.	A	B	.	.	.	0.77	-0.06	.	.	.	0.30	0.47
	Ala	998	.	A	0.42	0.37	.	.	.	0.24	0.47
	Asn	999	T	0.42	0.33	.	*	F	1.13	0.77
	Pro	1000	T	0.52	-0.36	.	*	F	2.22	1.50
60	Gly	1001	T	T	1.33	-0.10	*	*	F	2.76	2.32
	Ser	1002	.	.	B	.	T	T	1.92	-0.60	*	.	F	3.40	2.41
	Arg	1003	.	.	B	.	.	.	1.70	-1.00	*	*	F	2.46	2.60
	Tyr	1004	.	.	B	.	.	T	0.84	-0.74	*	*	F	2.51	2.17
	Asp	1005	.	.	B	.	.	T	0.76	-0.53	*	.	F	2.36	1.20

5	Asp	1006	.	.	B	.	.	T	.	1.21	-0.53	*	*	F	2.06	0.82
	Leu	1007	.	.	B	.	.	T	.	0.70	-0.53	*	.	F	2.06	1.03
	Val	1008	.	.	B	-0.22	-0.60	*	.	F	1.90	0.51
	Ser	1009	.	A	B	0.02	0.09	*	.	.	0.46	0.25
	Arg	1010	.	A	B	0.02	0.09	*	.	.	0.27	0.53
10	Leu	1011	.	A	B	-0.32	-0.20	*	*	F	0.98	1.23
	Leu	1012	.	A	B	0.14	-0.41	*	.	F	0.64	0.91
	Glu	1013	.	.	B	.	.	T	.	0.71	-0.37	*	.	F	0.85	0.46
	Gln	1014	T	T	.	0.80	0.54	*	*	F	0.35	0.58
	Gly	1015	T	T	.	0.34	0.29	*	*	F	0.80	1.09
15	Gly	1016	T	C	1.16	0.03	.	*	F	0.45	0.63
	Trp	1017	T	C	1.16	0.03	.	.	F	0.45	0.63
	Pro	1018	T	C	0.34	0.31	.	.	F	0.45	0.52
	Gly	1019	T	C	-0.24	0.57	.	*	F	0.15	0.43
	Glu	1020	.	.	B	.	.	T	.	-0.20	0.64	.	*	F	-0.05	0.42
20	Leu	1021	.	A	B	-0.14	0.11	.	*	.	-0.30	0.36
	Leu	1022	.	A	C	0.14	0.60	.	*	.	-0.40	0.38
	Ala	1023	.	A	C	-0.23	0.17	.	*	.	-0.10	0.38
	Ser	1024	.	A	C	0.11	0.67	.	*	.	-0.40	0.47
	Trp	1025	A	A	0.11	0.39	.	*	.	0.00	0.99
25	Glu	1026	A	A	0.62	-0.30	.	*	.	1.05	1.63
	Ala	1027	A	T	.	0.84	-0.41	.	*	.	1.75	1.63
	Gln	1028	T	C	1.43	-0.30	*	*	F	2.40	1.57
	Asp	1029	T	C	1.84	-1.21	*	.	F	3.00	1.57
	Ser	1030	T	C	2.13	-1.21	*	.	F	2.70	3.04
30	Ala	1031	C	1.82	-1.31	*	.	F	2.20	2.83
	Glu	1032	C	2.10	-1.23	*	.	F	1.90	2.44
	Arg	1033	T	.	.	1.80	-0.74	.	.	F	1.80	2.63
	Asn	1034	T	C	1.80	-0.74	.	.	F	1.50	3.49
	Thr	1035	T	C	2.10	-1.24	*	.	F	1.50	3.49
35	Thr	1036	T	C	2.69	-1.24	.	.	F	1.50	3.09
	Ser	1037	T	C	2.48	-1.24	.	.	F	1.50	3.20
	Glu	1038	C	2.02	-1.21	.	.	F	1.64	3.43
	Glu	1039	C	1.43	-1.27	.	.	F	1.98	2.35
	Asp	1040	T	C	1.74	-1.26	.	.	F	2.52	1.77
40	Pro	1041	T	C	2.06	-1.64	.	.	F	2.86	1.77
	Gly	1042	T	T	.	1.50	-1.24	.	.	F	3.40	1.77
	Ala	1043	A	T	.	0.69	-0.60	.	.	F	2.51	0.79
	Glu	1044	A	A	-0.12	0.09	.	.	F	0.87	0.42
	Gln	1045	A	A	-0.16	0.34	.	.	.	0.38	0.35
45	Val	1046	.	A	B	-0.76	0.41	*	.	.	-0.26	0.47
	Leu	1047	.	A	B	-0.62	0.60	.	*	.	-0.60	0.22
	Leu	1048	.	A	B	-0.73	1.03	.	*	.	-0.60	0.20
	His	1049	.	A	B	-1.04	1.41	.	*	.	-0.60	0.23
	Leu	1050	.	A	C	-1.64	1.26	.	*	.	-0.40	0.41
50	Pro	1051	.	A	C	-1.64	1.19	.	*	.	-0.40	0.49
	Phe	1052	.	.	B	B	.	.	.	-1.14	1.14	*	.	.	-0.60	0.27
	Thr	1053	.	.	B	B	.	.	.	-0.33	1.13	.	*	.	-0.60	0.47
	Met	1054	.	A	B	B	.	.	.	-0.30	0.44	.	*	.	-0.60	0.53
	Val	1055	.	A	B	B	.	.	.	0.62	0.41	.	.	.	-0.45	1.05
55	Thr	1056	.	A	B	B	.	.	.	0.94	-0.37	*	.	F	0.60	1.43
	Glu	1057	.	A	B	B	.	.	.	0.83	-0.86	.	*	F	0.90	2.83
	Gln	1058	.	A	B	1.14	-0.79	*	.	F	0.90	3.14
	Arg	1059	.	A	B	1.74	-1.43	*	.	F	0.90	3.63
	Arg	1060	.	A	B	1.71	-1.91	*	.	F	0.90	3.50
60	Leu	1061	.	A	B	1.21	-1.23	*	.	F	0.90	1.42
	Asp	1062	.	A	B	0.87	-0.94	*	.	F	0.75	0.60
	Asp	1063	.	A	B	0.87	-0.51	*	.	F	0.75	0.30
	Ile	1064	.	A	B	-0.06	-0.11	*	.	.	0.30	0.59
	Leu	1065	.	A	B	-0.47	-0.11	*	*	.	0.30	0.29
	Gly	1066	.	A	.	.	T	.	.	0.34	0.27	*	.	.	0.10	0.23
	Asn	1067	C	0.34	0.67	*	*	F	-0.05	0.58
	Leu	1068	C	0.13	0.39	*	*	F	0.40	1.21

	Ser	1069	C	1.02	0.13	*	*	F	0.40	1.89
	Gln	1070	.	A	C	1.83	-0.30	*	.	F	0.80	2.03
	Gln	1071	.	A	C	1.37	-0.70	.	*	F	1.10	4.27
	Pro	1072	.	A	B	1.48	-0.70	*	*	F	0.90	2.63
5	Glu	1073	.	A	B	2.29	-1.09	*	.	F	0.90	2.97
	Glu	1074	.	A	B	1.78	-1.49	*	.	F	0.90	2.87
	Leu	1075	.	A	B	1.53	-1.20	*	.	F	0.90	1.53
	Arg	1076	.	A	.	.	T	.	.	1.23	-0.87	*	.	F	1.30	1.38
	Asp	1077	.	A	.	.	T	.	.	1.49	-0.49	*	.	F	1.00	1.07
10	Leu	1078	A	A	1.46	-0.49	*	.	F	0.60	2.60
	Tyr	1079	.	A	.	.	T	.	.	0.64	-0.67	*	.	F	1.30	1.80
	Ser	1080	.	A	.	.	T	.	.	0.60	0.01	*	.	F	0.25	0.89
	Lys	1081	.	A	B	-0.10	0.66	.	.	.	-0.60	0.80
	His	1082	.	A	B	-0.10	0.47	.	*	.	-0.60	0.52
15	Leu	1083	.	A	B	-0.10	0.11	.	.	.	-0.30	0.67
	Val	1084	.	A	B	-0.44	0.41	*	.	.	-0.60	0.28
	Ala	1085	.	A	B	-0.14	0.91	*	.	.	-0.60	0.20
	Gln	1086	.	A	B	-0.19	0.81	*	.	.	-0.60	0.43
	Leu	1087	.	A	B	-1.04	0.13	*	.	.	-0.15	1.00
20	Ala	1088	A	A	-0.93	0.17	*	*	.	-0.30	0.70
	Gln	1089	A	A	0.03	0.46	*	.	.	-0.60	0.35
	Glu	1090	.	A	B	0.32	0.06	*	*	.	-0.30	0.83
	Ile	1091	.	A	B	0.29	-0.24	*	*	.	0.45	1.10
	Phe	1092	.	A	B	0.29	-0.24	*	*	.	0.30	0.86
25	Arg	1093	.	A	B	0.88	0.04	*	*	.	-0.30	0.41
	Ser	1094	.	A	C	0.84	0.04	*	*	.	0.05	1.01
	His	1095	.	A	C	0.84	-0.14	*	*	.	0.65	1.59
	Leu	1096	.	A	C	1.73	-0.53	*	*	.	0.95	1.41
	Glu	1097	.	A	C	2.12	-0.53	*	*	.	0.95	1.75
30	His	1098	T	T	.	1.20	-0.43	*	*	.	1.25	1.86
	Gln	1099	T	T	.	0.69	-0.24	*	.	F	1.40	1.86
	Asp	1100	T	T	.	0.77	-0.24	*	.	F	1.25	0.89
	Thr	1101	.	.	B	.	.	T	.	1.37	-0.24	*	.	F	1.30	1.30
	Leu	1102	C	1.07	-0.31	*	.	F	1.60	1.16
35	Leu	1103	C	1.10	-0.33	*	*	F	1.75	0.93
	Lys	1104	T	C	1.21	-0.33	*	.	F	2.40	1.12
	Pro	1105	T	C	1.32	-0.81	*	.	F	3.00	2.66
	Ser	1106	T	C	1.32	-1.50	*	.	F	2.70	6.31
	Glu	1107	T	T	.	1.83	-1.70	*	.	F	2.60	4.55
40	Arg	1108	T	.	.	2.43	-1.31	*	.	F	2.10	3.95
	Arg	1109	T	.	.	1.53	-1.31	*	.	F	1.80	4.55
	Thr	1110	.	.	B	B	.	.	.	1.43	-1.06	.	.	F	0.90	1.95
	Ser	1111	.	.	B	B	.	.	.	0.92	-0.57	.	.	F	0.90	1.44
	Pro	1112	.	.	B	B	.	.	.	0.62	0.11	.	.	F	-0.15	0.61
45	Val	1113	.	.	B	B	.	.	.	0.30	0.50	.	.	F	-0.45	0.56
	Thr	1114	.	.	B	B	.	.	.	0.16	0.44	.	.	F	-0.45	0.65
	Leu	1115	.	.	B	B	.	.	.	0.51	0.56	.	.	F	-0.25	0.57
	Ser	1116	.	.	B	.	.	T	.	0.78	0.13	.	.	F	0.80	1.54
	Pro	1117	.	.	B	.	.	T	.	0.13	-0.01	.	.	F	1.60	1.45
50	His	1118	T	T	.	0.69	0.14	.	.	F	1.60	1.31
	Lys	1119	.	.	B	.	.	T	.	0.66	-0.16	.	.	F	2.00	1.31
	His	1120	.	.	B	.	.	T	.	0.77	-0.11	.	.	.	1.50	0.84
	Val	1121	.	.	B	.	.	T	.	0.77	0.24	*	.	.	0.70	0.53
	Ser	1122	.	.	B	.	.	T	.	0.68	0.13	*	.	.	0.50	0.36
55	Gly	1123	.	.	B	.	.	T	.	0.41	0.51	*	.	F	0.15	0.35
	Phe	1124	.	.	B	-0.44	0.40	*	*	F	-0.25	0.63
	Ser	1125	.	.	B	.	.	T	.	-0.30	0.44	*	*	F	-0.05	0.39
	Ser	1126	.	.	B	.	.	T	.	0.24	0.06	*	*	F	0.25	0.77
	Ser	1127	.	.	B	.	.	T	.	0.24	0.11	*	*	F	0.40	1.29
60	Leu	1128	.	.	B	.	.	T	.	0.29	-0.29	*	*	F	1.26	1.29
	Arg	1129	.	.	B	0.68	-0.29	*	*	F	1.32	1.29
	Thr	1130	.	.	B	0.63	-0.19	.	*	F	1.58	1.39
	Ser	1131	T	C	0.93	-0.14	.	*	F	2.24	1.66

5	Ser	1132	.	.	B	.	.	T	.	0.64	-0.83	.	*	F	2.60	1.42
	Thr	1133	.	.	B	.	.	T	.	1.11	-0.33	.	*	F	1.89	0.99
	Gly	1134	.	.	B	.	.	T	.	0.66	-0.39	.	*	F	1.63	0.73
	Asp	1135	T	T	.	0.62	-0.34	.	.	F	1.77	0.54
	Ala	1136	T	C	0.62	-0.30	.	*	F	1.31	0.37
10	Gly	1137	T	T	.	1.03	-0.40	*	.	F	1.25	0.50
	Gly	1138	T	T	.	1.46	-0.83	*	.	F	1.55	0.59
	Gly	1139	C	1.59	-0.83	*	.	F	1.64	1.14
	Ser	1140	C	1.56	-0.90	*	.	F	1.98	1.78
	Arg	1141	.	.	B	2.26	-0.83	*	.	F	2.12	2.45
15	Arg	1142	.	.	B	.	.	T	.	2.64	-1.26	*	.	F	2.66	4.86
	Pro	1143	T	T	.	2.78	-1.69	*	.	F	3.40	7.25
	His	1144	T	T	.	2.81	-1.64	*	.	F	3.06	5.72
	Arg	1145	T	C	2.22	-1.16	*	.	F	2.52	4.22
	Lys	1146	.	.	B	B	.	.	.	1.30	-0.47	*	.	F	1.28	1.91
20	Pro	1147	.	.	B	B	.	.	.	1.30	-0.21	*	.	F	0.94	1.16
	Thr	1148	.	.	B	B	.	.	.	1.56	-0.71	*	.	F	0.90	1.16
	Ile	1149	.	.	B	B	.	.	.	0.70	-0.71	*	.	.	0.75	1.16
	Leu	1150	.	.	B	B	.	.	.	0.29	-0.03	*	.	.	0.30	0.53
	Arg	1151	.	.	B	B	.	.	.	-0.34	-0.07	*	.	F	0.45	0.49
25	Lys	1152	.	.	B	B	.	.	.	-0.72	-0.06	*	.	F	0.45	0.70
	Ile	1153	.	.	B	B	.	.	.	-0.41	-0.24	*	.	.	0.30	0.86
	Ser	1154	.	A	B	0.48	-0.53	*	.	.	0.60	0.76
	Ala	1155	.	A	B	0.48	-0.13	*	.	.	0.30	0.66
	Ala	1156	.	A	B	0.07	0.56	*	.	.	-0.60	0.78
30	Gln	1157	.	A	B	-0.57	0.26	.	*	.	-0.30	0.78
	Gln	1158	.	A	B	0.02	0.37	.	.	.	-0.30	0.78
	Leu	1159	.	A	C	0.32	0.26	.	.	.	0.05	1.03
	Ser	1160	.	A	C	0.06	-0.24	.	.	.	0.65	1.03
	Ala	1161	.	A	B	-0.21	0.00	.	.	F	-0.15	0.44
35	Ser	1162	.	A	B	B	.	.	.	-0.52	0.24	.	.	F	-0.15	0.40
	Glu	1163	.	A	B	B	.	.	.	-0.56	0.04	.	.	.	-0.30	0.43
	Val	1164	.	A	B	B	.	.	.	-0.56	0.16	*	.	.	-0.30	0.58
	Val	1165	.	A	B	B	.	.	.	-0.60	0.34	*	.	.	-0.30	0.35
	Thr	1166	.	A	B	B	.	.	.	-0.01	0.39	*	.	.	-0.30	0.20
40	His	1167	.	A	B	B	.	.	.	-0.02	0.79	*	.	.	-0.60	0.47
	Leu	1168	.	A	B	B	.	.	.	-0.88	0.63	*	.	F	-0.45	0.92
	Gly	1169	.	A	B	B	.	.	.	-0.61	0.63	*	.	F	-0.45	0.47
	Gln	1170	.	A	B	B	.	.	.	-0.57	0.64	*	.	F	-0.45	0.35
	Thr	1171	.	A	B	B	.	.	.	-0.84	0.83	.	.	F	-0.45	0.35
45	Val	1172	.	A	B	B	.	.	.	-1.11	0.64	.	.	.	-0.60	0.36
	Ala	1173	.	A	B	B	.	.	.	-0.64	0.60	.	.	.	-0.60	0.28
	Leu	1174	.	A	B	B	.	.	.	-0.61	0.63	.	.	.	-0.60	0.19
	Ala	1175	.	.	B	.	.	T	.	-1.42	0.63	.	.	.	-0.20	0.37
	Ser	1176	T	C	-1.41	0.67	.	*	F	0.15	0.30
50	Gly	1177	T	T	.	-1.41	0.56	.	.	F	0.35	0.49
	Thr	1178	.	.	B	.	.	T	.	-1.63	0.51	.	*	F	-0.05	0.36
	Leu	1179	.	A	B	-1.63	0.70	.	*	.	-0.60	0.22
	Ser	1180	.	A	B	-1.08	1.00	.	*	.	-0.60	0.18
	Val	1181	.	A	B	-1.44	1.07	.	*	.	-0.60	0.17
55	Leu	1182	.	A	B	-1.10	1.16	.	*	.	-0.60	0.11
	Leu	1183	.	A	B	-1.38	0.47	.	*	.	-0.60	0.15
	His	1184	.	A	B	-1.46	0.59	.	*	.	-0.60	0.20
	Cys	1185	.	A	B	-1.50	0.63	.	.	.	-0.60	0.17
	Glu	1186	.	A	B	-0.68	0.37	.	.	.	-0.30	0.20
60	Ala	1187	.	A	B	-0.08	0.19	.	*	.	-0.06	0.20
	Ile	1188	.	A	.	.	T	.	.	0.84	0.11	.	*	.	0.58	0.59
	Gly	1189	.	A	.	.	T	.	.	0.67	-0.46	.	*	.	1.42	0.66
	His	1190	T	C	1.02	-0.03	.	*	.	2.01	1.01
	Pro	1191	T	C	0.13	-0.04	*	*	F	2.40	2.09
60	Arg	1192	T	C	0.42	-0.04	.	*	F	2.16	1.48
	Pro	1193	T	C	1.02	-0.09	.	*	F	1.92	1.46
	Thr	1194	T	.	.	0.78	0.33	*	*	F	0.93	0.99

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	Ile	1195	.	.	B	.	.	.	0.92	0.40	*	*	.	-0.16	0.51
	Ser	1196	.	.	B	.	.	.	1.13	0.40	*	*	.	-0.10	0.65
	Trp	1197	.	.	B	.	.	.	0.68	0.37	*	*	.	0.50	0.72
5	Ala	1198	T	0.89	0.31	*	.	.	1.35	1.02
	Arg	1199	T	1.20	-0.37	*	.	F	2.40	1.31
	Asn	1200	T	1.23	-0.76	*	.	F	3.00	2.17
	Gly	1201	T	1.53	-1.03	*	*	F	2.70	1.59
	Glu	1202	1.12	-1.13	*	*	F	2.20	1.41
	Glu	1203	1.41	-0.34	.	*	F	1.45	0.76
10	Val	1204	.	.	B	.	.	.	1.30	-0.36	*	*	.	0.95	1.03
	Gln	1205	.	.	B	.	.	.	1.41	-0.79	*	*	.	0.80	0.99
	Phe	1206	.	.	B	.	.	T	0.87	-0.79	*	*	.	1.15	1.12
	Ser	1207	.	.	B	.	.	T	0.06	-0.10	*	*	.	0.85	1.06
	Asp	1208	.	.	B	.	.	T	-0.76	-0.06	*	*	.	0.70	0.50
15	Arg	1209	.	.	B	.	.	T	0.10	0.23	*	*	.	0.10	0.48
	Ile	1210	.	.	B	.	.	.	-0.11	-0.16	*	*	.	0.74	0.62
	Leu	1211	.	.	B	.	.	.	0.59	-0.11	*	*	.	0.98	0.57
	Leu	1212	.	.	B	.	.	.	0.89	-0.11	*	*	.	1.22	0.49
	Gln	1213	.	.	B	.	.	T	0.59	-0.11	*	*	.	1.81	1.16
20	Pro	1214	T	-0.33	-0.41	*	*	F	2.40	1.89
	Asp	1215	T	T	0.56	-0.41	.	*	F	2.36	1.89
	Asp	1216	T	T	0.48	-0.70	.	*	F	2.42	1.89
	Ser	1217	.	.	B	B	.	.	0.48	-0.41	.	*	.	0.78	0.86
25	Leu	1218	.	.	B	B	.	.	-0.11	-0.16	*	*	.	0.54	0.42
	Gln	1219	.	.	B	B	.	.	-0.11	0.34	*	*	.	-0.30	0.26
	Ile	1220	.	.	B	B	.	.	-0.97	0.77	*	*	.	-0.60	0.30
	Leu	1221	.	.	B	B	.	.	-0.97	1.03	.	*	.	-0.60	0.27
	Ala	1222	.	.	B	B	.	.	-1.26	0.34	.	*	.	-0.30	0.27
30	Pro	1223	.	A	B	.	.	.	-0.44	0.44	*	*	.	-0.60	0.38
	Val	1224	.	A	B	.	.	.	-1.30	-0.24	.	*	.	0.30	0.78
	Glu	1225	.	A	B	.	.	.	-0.76	-0.29	.	*	.	0.30	0.57
	Ala	1226	.	A	B	.	.	.	-0.64	-0.36	.	*	.	0.30	0.37
	Asp	1227	.	A	B	B	.	.	-0.30	0.00	.	*	.	-0.30	0.43
	Val	1228	.	A	B	B	.	.	-0.40	0.11	.	*	.	-0.30	0.39
35	Gly	1229	.	A	B	B	.	.	-0.21	0.60	.	*	.	-0.60	0.55
	Phe	1230	.	.	B	B	.	.	-0.21	0.67	.	*	.	-0.60	0.18
	Tyr	1231	.	.	B	.	.	T	-0.21	1.07	.	.	.	-0.20	0.38
	Thr	1232	.	.	B	.	.	T	-0.52	0.93	.	.	.	-0.20	0.39
	Cys	1233	.	.	B	.	.	T	0.33	0.99	.	.	.	-0.20	0.65
40	Asn	1234	T	T	0.09	0.60	.	.	.	0.20	0.67
	Ala	1235	.	.	B	.	.	.	-0.02	0.34	.	.	.	-0.10	0.47
	Thr	1236	.	.	B	.	.	.	-0.12	0.54	.	.	F	-0.25	0.72
	Asn	1237	.	.	B	.	.	.	-0.06	0.40	.	.	.	-0.40	0.44
45	Ala	1238	.	.	B	.	.	.	0.61	0.76	.	.	.	-0.40	0.69
	Leu	1239	.	.	B	.	.	.	0.31	0.26	.	.	.	-0.10	0.80
	Gly	1240	.	.	B	.	.	T	0.04	0.16	.	.	.	0.10	0.66
	Tyr	1241	.	.	B	.	.	T	0.06	0.40	.	.	.	-0.20	0.49
	Asp	1242	.	.	B	.	.	T	-0.83	0.29	.	.	F	0.25	0.79
	Ser	1243	.	.	B	.	.	T	-0.83	0.29	.	.	.	0.10	0.56
50	Val	1244	.	.	B	B	.	.	-0.88	0.36	.	.	.	-0.30	0.36
	Ser	1245	.	.	B	B	.	.	-0.84	0.24	.	*	.	-0.30	0.16
	Ile	1246	.	.	B	B	.	.	-1.41	0.73	.	*	.	-0.60	0.17
	Ala	1247	.	.	B	B	.	.	-2.00	1.03	.	*	.	-0.60	0.19
55	Val	1248	.	.	B	B	.	.	-2.04	0.89	.	*	.	-0.60	0.14
	Thr	1249	.	.	B	B	.	.	-1.14	0.93	*	*	.	-0.60	0.20
	Leu	1250	.	.	B	B	.	.	-1.06	0.24	.	*	.	-0.30	0.40
	Ala	1251	.	.	B	B	.	.	-0.98	0.17	.	*	.	-0.30	0.84
	Gly	1252	.	.	.	B	.	.	-1.24	0.21	*	*	F	0.05	0.48
	Lys	1253	.	.	.	B	.	.	-0.34	0.37	*	*	F	0.05	0.43
60	Pro	1254	.	.	B	B	.	.	-0.34	-0.31	*	*	F	0.45	0.86
	Leu	1255	.	.	B	B	.	.	0.17	-0.33	*	*	F	0.60	1.25
	Val	1256	.	.	B	B	.	.	0.87	-0.37	*	*	F	0.45	0.84
	Lys	1257	.	.	B	B	.	.	0.61	-0.37	*	*	F	0.60	1.06

5	Thr	1258	.	.	B	B	.	.	.	0.26	-0.19	*	*	F	0.60	1.28
	Ser	1259	.	.	B	B	.	.	.	-0.39	-0.39	.	.	F	0.60	2.48
	Arg	1260	.	.	B	B	.	.	.	-0.47	-0.39	.	.	F	0.45	0.92
	Met	1261	.	.	B	B	.	.	.	0.39	0.30	.	.	.	-0.30	0.45
	Thr	1262	.	.	B	B	.	.	.	0.03	0.21	.	.	.	-0.30	0.54
10	Val	1263	.	.	B	B	.	.	.	0.34	0.31	.	.	.	-0.30	0.40
	Ile	1264	.	.	B	B	.	.	.	0.69	0.31	.	.	.	0.00	0.69
	Asn	1265	.	.	B	.	.	T	.	0.37	-0.30	.	.	.	1.30	0.96
	Thr	1266	T	C	0.38	-0.36	.	.	F	2.10	2.00
	Glu	1267	T	C	-0.17	-0.50	*	.	F	2.40	2.88
15	Lys	1268	T	C	0.38	-0.54	*	.	F	3.00	1.33
	Pro	1269	.	.	.	B	.	.	C	0.41	-0.46	.	*	F	2.00	1.33
	Ala	1270	.	.	B	B	.	.	.	0.41	-0.30	.	*	.	1.20	0.57
	Val	1271	.	.	B	B	.	.	.	-0.17	-0.30	.	*	.	0.90	0.48
	Thr	1272	.	.	B	B	.	.	.	-0.51	0.39	.	*	.	0.00	0.22
20	Val	1273	.	.	B	B	.	.	.	-0.86	0.39	.	*	.	-0.30	0.21
	Asp	1274	.	.	B	.	.	T	.	-0.96	0.27	.	*	.	0.10	0.38
	Ile	1275	.	.	B	.	.	T	.	-1.26	0.11	*	*	F	0.25	0.38
	Gly	1276	.	.	B	.	.	T	.	-0.36	0.31	*	*	F	0.25	0.36
	Ser	1277	.	.	B	.	.	T	.	-0.36	-0.33	*	*	F	0.85	0.43
25	Thr	1278	.	.	B	B	.	.	.	-0.36	0.16	*	*	F	-0.15	0.89
	Ile	1279	.	.	B	B	.	.	.	-0.36	0.11	*	*	F	-0.15	0.67
	Lys	1280	.	.	B	B	.	.	.	0.19	0.09	*	.	F	-0.15	0.86
	Thr	1281	.	.	B	B	.	.	.	-0.32	0.13	*	.	F	-0.15	0.59
	Val	1282	.	.	B	B	.	.	.	-0.02	0.29	.	.	F	-0.15	0.62
30	Gln	1283	.	.	B	B	.	.	.	-0.57	0.00	.	.	F	-0.15	0.50
	Gly	1284	.	.	B	B	.	.	.	0.01	0.64	*	*	F	-0.45	0.26
	Val	1285	.	.	B	B	.	.	.	-0.92	0.64	*	*	.	-0.60	0.50
	Asn	1286	.	.	B	B	.	.	.	-0.61	0.69	*	*	.	-0.60	0.20
	Val	1287	.	.	B	B	.	.	.	-0.42	0.69	.	*	.	-0.60	0.33
35	Thr	1288	.	.	B	B	.	.	.	-0.42	0.83	.	*	.	-0.60	0.24
	Ile	1289	.	.	B	B	.	.	.	-0.93	0.59	.	*	.	-0.60	0.26
	Asn	1290	.	.	B	B	.	.	.	-0.67	0.83	.	*	.	-0.60	0.26
	Cys	1291	.	.	B	B	.	.	.	-1.01	0.69	.	*	.	-0.60	0.18
	Gln	1292	.	.	B	B	.	.	.	-1.01	0.63	.	*	.	-0.60	0.25
40	Val	1293	.	.	B	B	.	.	.	-0.91	0.59	.	*	.	-0.60	0.12
	Ala	1294	.	.	B	B	.	.	.	-0.02	0.61	.	*	.	-0.60	0.34
	Gly	1295	.	.	.	B	.	.	C	-0.61	0.04	.	*	.	-0.10	0.34
	Val	1296	C	0.06	0.14	.	*	.	0.10	0.46
	Pro	1297	.	.	B	-0.80	-0.50	.	*	F	0.65	0.79
45	Glu	1298	.	.	B	-0.26	-0.36	.	*	F	0.65	0.59
	Ala	1299	.	.	B	B	.	.	.	0.04	-0.30	.	.	F	0.60	1.15
	Glu	1300	.	.	B	B	.	.	.	-0.31	-0.03	*	.	.	0.30	0.78
	Val	1301	A	.	.	B	.	.	.	0.66	0.33	*	.	.	-0.30	0.39
	Thr	1302	A	.	.	B	.	.	.	0.87	0.33	.	*	.	0.04	0.76
50	Trp	1303	A	.	.	B	.	.	.	0.91	0.23	.	*	.	0.38	0.70
	Phe	1304	A	.	.	B	.	.	.	1.20	0.23	.	*	.	0.87	1.90
	Arg	1305	.	.	.	B	T	.	.	1.24	-0.03	*	*	F	2.36	1.76
	Asn	1306	T	T	.	1.29	-0.51	*	*	F	3.40	3.35
	Lys	1307	T	T	.	1.26	-0.74	*	*	F	3.06	3.19
55	Ser	1308	T	T	.	1.24	-1.10	*	*	F	2.93	1.61
	Lys	1309	T	T	.	1.73	-0.71	*	*	F	2.80	1.34
	Leu	1310	T	.	.	1.59	-0.69	*	*	F	2.47	1.04
	Gly	1311	C	1.56	-0.19	.	*	F	1.84	1.05
	Ser	1312	T	C	0.70	-0.07	.	*	F	2.10	0.72
60	Pro	1313	.	.	B	.	.	T	.	0.97	0.61	.	.	F	0.79	0.72
	His	1314	.	.	B	.	.	T	.	0.92	0.43	.	.	.	0.43	0.99
	His	1315	.	.	B	.	.	T	.	1.39	0.00	.	.	.	0.67	1.28
	Leu	1316	.	.	B	1.43	0.04	.	.	.	0.11	0.82
	His	1317	.	.	B	.	.	T	.	0.92	0.00	.	.	.	0.10	0.80
60	Glu	1318	.	.	B	.	.	T	.	0.32	0.19	.	.	F	0.25	0.49
	Gly	1319	T	T	.	-0.46	0.37	.	.	F	0.65	0.49
	Ser	1320	.	.	B	.	.	T	.	-0.73	0.37	.	.	F	0.25	0.30

	Leu	1321	.	.	B	B	.	.	.	0.08	0.36	*	.	F	-0.15	0.25
	Leu	1322	.	.	B	B	.	.	.	-0.74	0.76	.	.	.	-0.60	0.40
	Leu	1323	.	.	B	B	.	.	.	-1.04	0.97	.	.	.	-0.60	0.22
	Thr	1324	.	.	B	B	.	.	.	-1.00	0.97	.	.	.	-0.60	0.36
5	Asn	1325	.	.	B	B	.	.	.	-1.00	0.67	.	.	F	-0.17	0.58
	Val	1326	.	.	B	B	.	.	.	-0.19	0.37	.	.	F	0.41	0.95
	Ser	1327	.	.	B	0.62	-0.31	.	.	F	1.64	1.10
	Ser	1328	.	.	B	.	.	T	.	1.09	-0.40	.	.	F	2.12	1.18
	Ser	1329	T	T	.	0.59	-0.37	.	.	F	2.80	1.58
10	Asp	1330	T	T	.	0.34	-0.33	.	.	F	2.37	0.97
	Gln	1331	T	T	.	0.90	0.04	.	.	F	1.64	1.14
	Gly	1332	T	.	.	0.53	0.04	*	.	F	1.16	1.14
	Leu	1333	.	.	B	0.94	0.23	.	*	.	0.18	0.36
	Tyr	1334	.	.	B	.	.	T	.	0.66	0.23	*	*	.	0.10	0.41
15	Ser	1335	.	.	B	.	.	T	.	0.07	0.33	*	.	.	0.10	0.42
	Cys	1336	.	.	B	.	.	T	.	0.07	0.40	.	.	.	-0.20	0.52
	Arg	1337	.	.	B	.	.	T	.	-0.40	0.11	.	.	.	0.10	0.53
	Ala	1338	.	A	B	0.38	0.04	.	.	.	-0.30	0.33
20	Ala	1339	.	A	B	0.28	0.16	*	*	.	-0.30	0.83
	Asn	1340	.	A	C	0.58	0.01	*	*	.	-0.10	0.42
	Leu	1341	.	A	C	0.43	0.01	*	*	.	-0.10	0.72
	His	1342	.	A	C	0.01	0.20	*	*	.	-0.10	0.58
	Gly	1343	.	A	C	0.60	0.19	*	*	.	-0.10	0.52
	Glu	1344	.	A	C	0.89	-0.21	.	*	F	0.80	1.10
25	Leu	1345	.	A	C	0.58	-0.51	*	*	F	1.10	1.09
	Thr	1346	.	A	B	1.39	-0.53	.	*	F	0.90	1.58
	Glu	1347	.	A	B	0.61	-0.56	.	*	F	0.90	1.58
	Ser	1348	.	.	B	B	.	.	.	0.14	0.13	.	*	F	0.00	1.58
	Thr	1349	.	.	B	B	.	.	.	-0.74	0.13	.	.	F	-0.15	0.90
30	Gln	1350	.	.	B	B	.	.	.	-0.74	0.33	.	.	F	-0.15	0.37
	Leu	1351	.	.	B	B	.	.	.	-0.43	1.01	.	.	.	-0.60	0.23
	Leu	1352	.	.	B	B	.	.	.	-0.64	0.63	.	.	.	-0.60	0.26
	Ile	1353	.	.	B	B	.	.	.	-0.56	0.57	.	.	.	-0.60	0.23
	Leu	1354	.	.	B	B	.	.	.	-0.24	0.60	.	.	.	-0.60	0.44
35	Asp	1355	T	C	-1.10	0.31	.	.	F	0.45	0.92
	Pro	1356	T	C	-0.50	0.27	.	.	F	0.45	0.97
	Pro	1357	T	T	.	0.00	0.01	*	.	F	0.80	1.82
	Gln	1358	T	C	0.89	-0.19	*	*	F	1.20	1.57
	Val	1359	.	.	B	0.89	0.21	.	*	F	0.20	1.76
40	Pro	1360	.	.	B	0.89	0.47	*	*	F	-0.25	0.94
	Thr	1361	.	A	B	1.10	0.04	*	*	F	-0.15	0.94
	Gln	1362	.	A	B	0.42	-0.36	*	*	F	0.60	2.11
	Leu	1363	.	A	B	0.53	-0.31	*	*	F	0.45	0.96
	Glu	1364	.	A	B	0.80	-0.74	*	*	F	0.90	1.30
45	Asp	1365	.	A	B	0.20	-0.73	*	*	F	0.75	0.76
	Ile	1366	.	A	B	-0.30	-0.44	*	*	.	0.30	0.76
	Arg	1367	.	A	B	-0.89	-0.44	.	*	.	0.30	0.36
	Ala	1368	.	A	B	-0.67	0.06	*	*	.	-0.30	0.22
	Leu	1369	.	A	B	-0.98	0.56	*	*	.	-0.60	0.31
50	Leu	1370	.	A	B	-1.32	0.36	.	*	.	-0.30	0.23
	Ala	1371	.	A	B	-0.64	0.79	.	*	.	-0.60	0.23
	Ala	1372	.	A	B	-0.76	0.71	.	*	.	-0.60	0.43
	Thr	1373	.	A	C	-0.98	0.43	.	.	F	-0.25	0.83
	Gly	1374	T	C	-0.38	0.43	.	.	F	0.15	0.68
55	Pro	1375	T	C	0.13	0.36	.	.	F	0.60	1.04
	Asn	1376	T	C	-0.13	0.24	.	.	F	0.45	0.96
	Leu	1377	.	.	B	.	.	T	.	-0.36	0.40	.	.	F	-0.05	0.72
	Pro	1378	.	.	B	B	.	.	.	-0.36	0.66	*	.	F	-0.45	0.39
	Ser	1379	.	.	B	B	.	.	.	-0.31	0.71	*	.	F	-0.45	0.35
60	Val	1380	.	.	B	B	.	.	.	-0.31	0.70	*	.	F	-0.45	0.56
	Leu	1381	.	.	B	B	.	.	.	-1.12	0.44	*	.	F	-0.45	0.56
	Thr	1382	.	.	B	B	.	.	.	-0.66	0.70	.	.	F	-0.45	0.35
	Ser	1383	.	.	B	.	.	T	.	-0.76	0.74	.	.	F	-0.05	0.46

	Pro	1384	.	.	B	.	.	T	.	-0.46	0.59	.	.	F	-0.05	0.81
	Leu	1385	T	T	.	-0.41	0.30	.	.	F	0.65	0.97
	Gly	1386	.	.	B	.	.	T	.	-0.46	0.50	.	.	F	-0.05	0.60
5	Thr	1387	.	.	B	B	.	.	.	-0.96	0.76	.	*	F	-0.45	0.29
	Gln	1388	.	.	B	B	.	.	.	-0.66	1.01	.	*	F	-0.45	0.29
	Leu	1389	.	.	B	B	.	.	.	-0.66	0.33	.	.	.	-0.30	0.48
	Val	1390	.	.	B	B	.	.	.	-0.19	0.33	*	.	.	-0.02	0.52
	Leu	1391	.	.	B	B	.	.	.	0.16	0.27	*	.	F	0.41	0.30
	Asp	1392	.	.	B	.	.	T	.	0.17	0.27	*	.	F	1.09	0.58
10	Pro	1393	T	T	.	-0.42	-0.03	*	.	F	2.52	1.04
	Gly	1394	T	T	.	-0.42	-0.17	.	.	F	2.80	1.28
	Asn	1395	T	T	.	-0.38	-0.17	*	.	F	2.37	0.63
	Ser	1396	.	.	B	0.09	0.51	.	.	F	0.59	0.34
	Ala	1397	.	.	B	-0.58	0.51	.	.	.	0.16	0.34
15	Leu	1398	.	.	B	-0.58	0.66	.	.	.	-0.12	0.11
	Leu	1399	.	.	B	-1.12	0.69	.	*	.	-0.40	0.13
	Gly	1400	.	.	B	-1.08	0.99	.	*	.	-0.40	0.09
	Cys	1401	.	.	B	-1.12	0.49	.	*	.	-0.40	0.22
20	Pro	1402	.	.	B	-0.57	0.23	.	*	.	-0.10	0.26
	Ile	1403	T	.	.	0.03	0.04	.	*	.	0.30	0.36
	Lys	1404	.	.	B	-0.01	0.04	.	*	F	0.20	1.03
	Gly	1405	.	.	B	0.12	0.11	.	*	F	0.05	0.50
	His	1406	.	.	B	.	.	T	.	0.79	0.11	.	*	F	0.40	1.10
25	Pro	1407	T	C	0.11	-0.17	.	*	.	0.90	0.88
	Val	1408	T	C	0.69	0.51	.	*	.	0.00	0.62
	Pro	1409	.	.	B	.	.	T	.	0.36	0.57	.	*	F	-0.05	0.66
	Asn	1410	.	.	B	B	.	.	.	0.00	0.99	.	.	.	-0.60	0.45
	Ile	1411	.	.	B	B	.	.	.	0.00	1.34	.	.	.	-0.60	0.53
30	Thr	1412	.	.	B	B	.	.	.	-0.13	1.20	.	.	.	-0.60	0.46
	Trp	1413	.	.	B	B	.	.	.	0.38	1.20	.	.	.	-0.60	0.28
	Phe	1414	.	.	B	B	.	.	.	0.59	1.23	.	.	.	-0.60	0.40
	His	1415	T	T	.	0.38	0.94	.	.	.	0.20	0.48
	Gly	1416	T	T	.	0.38	0.89	.	.	F	0.35	0.71
35	Gly	1417	T	C	-0.17	0.66	*	.	F	0.15	0.57
	Gln	1418	T	C	-0.19	0.51	*	.	F	0.15	0.31
	Pro	1419	.	.	.	B	.	.	C	-0.08	0.50	*	.	F	-0.25	0.46
	Ile	1420	.	.	B	B	.	.	.	-0.36	0.57	*	.	.	-0.60	0.47
	Val	1421	.	.	B	B	.	.	.	-0.36	0.63	.	.	.	-0.60	0.39
40	Thr	1422	.	.	B	B	.	.	.	-0.82	0.66	.	.	.	-0.60	0.25
	Ala	1423	.	.	B	B	.	.	.	-1.13	0.91	.	.	.	-0.60	0.29
	Thr	1424	.	.	B	B	.	.	.	-0.96	0.71	.	.	F	-0.45	0.57
	Gly	1425	.	.	B	B	.	.	.	-0.10	0.57	.	.	F	-0.45	0.54
	Leu	1426	.	.	B	B	.	.	.	-0.13	0.59	.	.	.	-0.60	0.72
45	Thr	1427	.	.	B	B	.	.	.	-0.63	0.77	.	.	.	-0.60	0.35
	His	1428	.	.	B	B	.	.	.	-0.63	0.97	.	.	.	-0.60	0.29
	His	1429	.	.	B	B	.	.	.	-0.91	1.04	.	.	.	-0.60	0.36
	Ile	1430	.	.	B	B	.	.	.	-0.91	0.86	.	.	.	-0.60	0.25
	Leu	1431	.	.	B	B	.	.	.	-0.10	0.80	*	*	.	-0.60	0.18
50	Ala	1432	.	.	B	B	.	.	.	-0.68	0.70	*	.	.	-0.60	0.23
	Ala	1433	.	.	B	B	.	.	.	-1.46	0.89	*	.	.	-0.60	0.23
	Gly	1434	.	.	B	B	.	.	.	-1.42	0.89	.	.	.	-0.60	0.23
	Gln	1435	.	.	B	B	.	.	.	-1.39	0.60	*	.	.	-0.60	0.40
	Ile	1436	.	.	B	B	.	.	.	-1.17	0.74	*	.	.	-0.60	0.29
55	Leu	1437	.	.	B	B	.	.	.	-0.58	0.74	*	.	.	-0.60	0.30
	Gln	1438	.	.	B	B	.	.	.	-0.80	0.71	*	.	.	-0.60	0.28
	Val	1439	.	.	B	B	.	.	.	-0.76	1.00	.	.	.	-0.60	0.33
	Ala	1440	.	.	B	B	.	.	.	-1.10	0.70	.	.	.	-0.60	0.53
	Asn	1441	.	.	B	B	.	.	.	-0.56	0.44	.	.	.	-0.60	0.30
60	Leu	1442	T	C	-0.04	0.47	.	.	F	0.15	0.40
	Ser	1443	T	C	-0.04	0.21	.	.	F	0.45	0.53
	Gly	1444	T	T	.	0.47	0.11	.	*	F	0.89	0.58
	Gly	1445	T	C	1.06	0.14	.	*	F	0.93	0.69
	Ser	1446	T	C	0.36	-0.54	.	*	F	2.07	0.89

	Gln	1447	T	C	0.87	-0.14	.	*	F	2.01	0.78
	Gly	1448	T	C	0.50	-0.19	.	.	F	2.40	1.06
	Glu	1449	.	.	B	.	.	T	.	0.03	-0.04	.	*	F	1.81	0.42
5	Phe	1450	.	A	B	-0.21	0.26	.	*	.	0.42	0.20
	Ser	1451	.	A	B	0.09	0.36	.	*	.	0.18	0.21
	Cys	1452	.	A	B	0.09	0.33	.	*	.	-0.06	0.21
	Leu	1453	.	A	B	0.43	0.73	.	*	.	-0.60	0.38
	Ala	1454	.	A	C	-0.16	-0.06	.	.	.	0.50	0.49
10	Gln	1455	.	A	C	0.20	0.06	.	.	F	0.05	0.93
	Asn	1456	.	A	C	-0.36	-0.09	.	.	F	0.80	1.12
	Glu	1457	A	A	-0.50	-0.13	.	.	F	0.45	0.82
	Ala	1458	A	A	-0.29	0.06	.	.	F	-0.15	0.39
	Gly	1459	.	A	B	0.30	0.27	.	.	.	-0.30	0.24
	Val	1460	.	A	B	0.34	0.27	*	.	.	-0.30	0.24
15	Leu	1461	.	A	B	-0.24	0.27	*	.	.	-0.30	0.48
	Met	1462	.	A	B	-0.54	0.27	.	.	.	-0.30	0.49
	Gln	1463	.	A	B	-0.77	0.23	.	.	.	-0.30	0.88
	Lys	1464	.	A	B	-1.28	0.27	.	.	.	-0.30	0.88
20	Ala	1465	.	A	B	B	.	.	.	-1.31	0.23	*	*	.	-0.30	0.66
	Ser	1466	.	A	B	B	.	.	.	-0.50	0.30	*	*	.	-0.30	0.27
	Leu	1467	.	A	B	B	.	.	.	0.10	0.30	*	.	.	-0.30	0.23
	Val	1468	.	A	B	B	.	.	.	-0.14	0.30	*	*	.	-0.30	0.38
	Ile	1469	.	A	B	B	.	.	.	-0.48	0.56	.	*	.	-0.60	0.45
25	Gln	1470	.	.	B	.	.	T	.	-0.18	1.09	.	.	.	-0.20	0.57
	Asp	1471	.	.	B	.	.	T	.	-0.18	1.31	.	.	.	-0.20	0.81
	Tyr	1472	T	T	.	-0.22	1.06	.	.	.	0.35	1.54
	Trp	1473	T	T	.	0.63	1.01	*	.	.	0.20	0.66
	Trp	1474	.	.	B	1.63	0.61	*	.	.	-0.40	0.66
30	Ser	1475	.	.	B	.	.	T	.	0.82	0.61	*	.	.	-0.20	0.82
	Val	1476	.	.	B	.	.	T	.	0.23	0.54	*	.	.	-0.20	0.65
	Asp	1477	T	T	.	0.17	0.13	*	.	F	0.65	0.62
	Arg	1478	T	T	.	-0.21	-0.30	*	.	.	1.10	0.67
	Leu	1479	T	T	.	-0.22	-0.11	*	.	.	0.90	0.48
35	Ala	1480	T	T	.	-0.51	-0.37	*	.	.	1.10	0.39
	Thr	1481	T	T	.	0.04	0.13	*	.	.	0.50	0.20
	Cys	1482	.	.	B	.	.	T	.	-0.62	0.51	*	.	.	0.05	0.33
	Ser	1483	.	.	B	.	.	T	.	-1.08	0.40	*	.	.	0.30	0.17
	Ala	1484	.	.	B	-0.27	0.33	*	.	.	0.65	0.12
40	Ser	1485	T	.	.	0.43	0.24	*	*	.	1.30	0.35
	Cys	1486	T	T	.	0.40	-0.33	*	.	F	2.50	0.52
	Gly	1487	T	T	.	0.21	-0.29	*	.	F	2.25	0.51
	Asn	1488	T	T	.	0.51	-0.14	*	.	F	2.00	0.28
	Arg	1489	T	T	.	1.10	-0.13	*	.	F	1.75	0.91
45	Gly	1490	T	.	.	1.19	-0.30	*	*	F	1.45	1.59
	Val	1491	.	.	B	1.97	-0.30	*	*	F	1.06	1.53
	Gln	1492	.	.	B	1.50	-0.70	*	*	F	1.62	1.53
	Gln	1493	.	.	B	.	.	T	.	1.61	-0.01	*	*	F	1.78	1.27
	Pro	1494	.	.	B	.	.	T	.	0.83	-0.44	*	*	F	2.04	3.36
50	Arg	1495	.	.	B	.	.	T	.	0.37	-0.51	.	*	F	2.60	1.04
	Lcu	1496	.	.	B	.	.	T	.	0.41	-0.23	.	*	.	1.74	0.50
	Arg	1497	.	A	B	0.41	0.06	.	*	.	0.48	0.26
	Cys	1498	.	A	B	0.11	0.03	*	*	.	0.22	0.22
	Leu	1499	.	A	B	0.01	0.41	*	*	.	-0.34	0.35
55	Leu	1500	.	A	B	-0.10	0.21	.	*	.	-0.30	0.26
	Asn	1501	.	.	B	.	.	T	.	-0.14	0.21	*	*	F	0.25	0.84
	Ser	1502	T	C	-0.26	0.29	*	*	F	0.45	0.76
	Thr	1503	T	T	.	0.20	0.00	.	.	F	0.80	1.47
	Glu	1504	T	T	.	0.42	-0.26	.	.	F	1.40	1.42
60	Val	1505	.	.	B	1.20	-0.16	.	.	F	0.80	1.07
	Asn	1506	.	.	B	.	.	T	.	0.53	-0.04	.	.	F	1.22	1.01
	Pro	1507	.	.	B	.	.	T	.	0.24	0.04	.	.	.	0.54	0.31
	Ala	1508	.	.	B	.	T	T	.	0.21	0.54	*	.	.	0.86	0.42
	His	1509	T	T	.	0.26	0.33	.	*	.	1.38	0.26

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	Cys	1510	T	T	.	0.26	-0.07	.	*	.	2.20	0.34
	Ala	1511	T	T	.	0.37	0.14	.	*	.	1.38	0.25
	Gly	1512	T	T	.	0.37	-0.36	.	*	.	1.76	0.36
5	Lys	1513	T	T	.	0.37	-0.43	.	*	F	1.84	1.03
	Val	1514	.	.	B	-0.46	-0.50	*	*	F	1.02	1.03
	Arg	1515	.	.	B	0.21	-0.36	*	*	F	0.65	0.77
	Pro	1516	.	.	B	0.59	-0.39	*	*	F	0.65	0.67
	Ala	1517	.	.	B	0.04	0.04	*	*	.	0.05	1.39
10	Val	1518	.	.	B	-0.59	0.09	*	*	.	-0.10	0.50
	Gln	1519	.	.	B	-0.40	0.59	*	*	.	-0.40	0.33
	Pro	1520	.	.	B	-0.51	0.73	*	*	.	-0.40	0.17
	Ile	1521	.	.	B	-0.19	0.63	*	.	.	-0.40	0.37
	Ala	1522	.	.	B	0.51	-0.01	*	.	.	0.84	0.42
15	Cys	1523	.	.	B	1.37	-0.41	.	.	.	1.18	0.54
	Asn	1524	.	.	B	.	.	T	.	0.70	-0.84	.	.	.	2.17	1.28
	Arg	1525	T	T	.	0.70	-0.96	.	.	F	2.91	0.68
	Arg	1526	T	T	.	1.29	-1.03	.	*	F	3.40	1.96
	Asp	1527	T	T	.	1.99	-1.21	.	*	F	3.06	1.63
20	Cys	1528	T	C	2.37	-1.61	.	.	F	2.52	1.63
	Pro	1529	T	T	.	1.77	-0.70	.	*	F	2.23	0.88
	Ser	1530	T	T	.	0.80	-0.09	.	*	F	1.59	0.52
	Arg	1531	.	.	B	.	.	T	.	0.38	0.56	.	*	F	-0.05	0.72
	Trp	1532	.	.	B	B	.	.	.	0.08	0.47	*	*	.	-0.60	0.67
25	Met	1533	.	.	B	B	.	.	.	0.46	0.43	*	*	.	-0.60	0.67
	Val	1534	.	.	B	B	.	.	.	0.37	0.96	*	*	.	-0.60	0.36
	Thr	1535	.	.	B	.	.	T	.	0.08	1.34	*	*	.	-0.20	0.46
	Ser	1536	T	T	.	-0.70	0.93	*	*	.	0.20	0.47
	Trp	1537	T	T	.	-0.72	0.89	*	*	.	0.20	0.34
30	Ser	1538	T	T	.	-0.01	0.73	*	*	.	0.20	0.34
	Ala	1539	T	.	.	0.54	0.24	*	*	.	0.55	0.49
	Cys	1540	T	T	.	0.19	0.24	*	*	.	1.00	0.63
	Thr	1541	.	.	B	.	.	T	.	0.14	-0.10	.	*	.	1.45	0.25
	Arg	1542	T	T	.	0.09	-0.06	*	*	F	2.25	0.25
35	Ser	1543	T	T	.	0.04	-0.13	*	.	F	2.50	0.46
	Cys	1544	T	T	.	-0.22	-0.27	*	.	F	2.25	0.31
	Gly	1545	T	T	.	0.44	-0.11	*	.	F	2.00	0.12
	Gly	1546	T	T	.	0.44	0.29	.	*	F	1.15	0.15
	Gly	1547	T	T	.	0.44	0.39	.	.	F	0.90	0.41
40	Val	1548	.	.	B	B	.	.	.	0.86	-0.19	.	.	F	0.45	0.82
	Gln	1549	.	.	B	B	.	.	.	0.67	-0.61	.	.	F	0.90	1.61
	Thr	1550	.	.	B	B	.	.	.	0.70	-0.40	.	.	F	0.60	1.21
	Arg	1551	.	.	B	B	.	.	.	0.38	-0.34	*	.	F	0.60	2.35
	Arg	1552	.	.	B	B	.	.	.	0.72	-0.41	.	.	F	0.45	0.73
45	Val	1553	.	.	B	B	.	.	.	1.62	-0.41	.	.	.	0.30	0.87
	Thr	1554	.	.	B	B	.	.	.	0.81	-0.90	*	.	.	0.60	0.89
	Cys	1555	.	.	B	B	.	.	.	1.17	-0.21	*	*	.	0.30	0.38
	Gln	1556	.	.	B	B	.	.	.	0.47	-0.21	*	*	F	0.60	1.01
	Lys	1557	.	.	B	B	.	.	.	0.06	-0.36	*	*	F	0.45	0.71
50	Leu	1558	.	.	B	0.57	-0.46	.	.	F	0.80	1.77
	Lys	1559	.	.	B	.	.	T	.	-0.01	-0.60	.	*	F	1.30	1.01
	Ala	1560	.	.	B	.	.	T	.	0.36	-0.31	.	*	F	0.85	0.36
	Ser	1561	.	.	B	.	.	T	.	0.04	0.07	.	*	F	0.25	0.58
	Gly	1562	.	.	B	.	.	T	.	-0.21	-0.13	.	*	F	0.85	0.42
55	Ile	1563	.	.	B	B	.	.	.	-0.26	0.30	.	*	F	0.13	0.64
	Ser	1564	.	.	B	B	.	.	.	-0.60	0.44	.	.	F	0.11	0.35
	Thr	1565	.	.	B	B	.	.	.	-0.01	0.44	.	.	F	0.39	0.48
	Pro	1566	.	.	B	0.29	0.41	.	.	F	1.02	1.10
	Val	1567	T	T	.	0.03	-0.27	.	.	F	2.80	1.37
60	Ser	1568	T	T	.	0.26	-0.04	.	.	F	2.37	0.94
	Asn	1569	T	T	.	0.24	0.04	.	.	F	1.49	0.32
	Asp	1570	T	T	.	0.56	0.10	*	*	F	1.21	0.63
	Met	1571	.	.	B	B	.	.	.	-0.09	-0.14	.	.	.	0.58	0.82
	Cys	1572	.	.	B	B	.	.	.	0.18	0.11	*	.	.	-0.30	0.38

5	Thr	1573	.	.	B	B	.	.	.	0.52	0.21	*	.	.	-0.30	0.23
	Gln	1574	.	.	B	B	.	.	.	0.63	0.21	*	.	.	-0.30	0.46
	Val	1575	.	.	B	B	.	.	.	0.42	-0.40	*	.	.	0.45	1.68
	Ala	1576	.	.	B	B	.	.	.	0.17	-0.54	*	.	F	1.20	1.80
	Lys	1577	.	.	B	0.83	-0.39	*	.	F	1.25	0.77
10	Arg	1578	.	.	B	0.83	-0.79	*	.	F	2.00	1.74
	Pro	1579	.	.	B	0.83	-0.94	*	.	F	2.30	2.48
	Val	1580	T	.	.	1.10	-1.04	*	.	F	3.00	2.15
	Asp	1581	.	A	B	1.02	-0.54	*	.	F	2.10	1.11
	Thr	1582	.	A	B	0.98	0.03	.	.	F	0.75	0.38
15	Gln	1583	.	A	B	0.87	0.00	.	.	F	0.45	0.83
	Ala	1584	.	A	B	1.08	-0.24	.	*	.	0.60	0.86
	Cys	1585	.	A	.	.	T	.	.	1.12	0.16	.	*	.	0.25	1.04
	Asn	1586	.	A	.	.	T	.	.	0.46	0.36	.	.	F	0.25	0.49
	Gln	1587	.	A	B	-0.09	0.53	.	*	F	-0.45	0.26
20	Gln	1588	.	A	B	-0.09	0.67	.	*	F	-0.45	0.36
	Leu	1589	.	A	B	0.21	0.10	.	*	.	-0.30	0.39
	Cys	1590	.	A	B	0.29	0.61	.	*	.	-0.60	0.24
	Val	1591	.	A	B	-0.41	0.71	.	*	.	-0.60	0.14
	Glu	1592	.	A	B	-0.71	1.10	.	*	.	-0.60	0.15
25	Trp	1593	.	A	B	-1.01	0.80	.	*	.	-0.60	0.36
	Ala	1594	.	A	B	-0.49	0.61	.	*	.	-0.60	0.66
	Phe	1595	T	T	.	-0.17	0.89	*	*	.	0.20	0.40
	Ser	1596	T	T	.	0.69	1.31	*	*	.	0.20	0.37
	Ser	1597	T	T	.	0.02	0.80	.	*	.	0.20	0.64
30	Trp	1598	T	T	.	0.31	0.87	.	.	.	0.20	0.40
	Gly	1599	T	T	.	0.56	0.49	.	.	F	0.35	0.48
	Gln	1600	T	T	.	1.04	0.53	.	*	F	0.35	0.35
	Cys	1601	T	T	.	0.68	0.57	.	.	F	0.35	0.52
	Asn	1602	T	T	.	0.09	0.23	.	.	F	0.65	0.28
35	Gly	1603	T	C	0.03	0.49	.	.	F	0.15	0.11
	Pro	1604	T	T	.	0.17	0.51	.	.	F	0.35	0.21
	Cys	1605	T	T	.	0.13	0.37	.	.	.	0.50	0.20
	Ile	1606	.	.	B	.	.	T	.	-0.01	0.47	.	.	.	-0.20	0.28
	Gly	1607	.	.	B	.	.	T	.	-0.60	0.73	.	.	.	-0.20	0.15
40	Pro	1608	.	.	B	.	.	T	.	-1.11	0.80	.	*	.	-0.20	0.28
	His	1609	.	.	B	.	.	T	.	-0.90	0.87	.	*	.	-0.20	0.30
	Leu	1610	.	.	B	.	.	T	.	-0.27	0.59	.	*	.	-0.20	0.52
	Ala	1611	.	.	B	B	.	.	.	0.73	0.66	.	*	.	-0.60	0.45
	Val	1612	.	.	B	B	.	.	.	1.08	0.23	.	*	.	-0.30	0.65
45	Gln	1613	.	.	B	B	.	.	.	0.43	0.13	*	*	.	-0.15	1.37
	His	1614	.	.	B	B	.	.	.	-0.23	0.09	.	*	.	-0.15	1.01
	Arg	1615	.	.	B	B	.	.	.	-0.09	0.37	.	*	.	-0.15	1.18
	Gln	1616	.	.	B	B	.	.	.	0.50	0.30	.	.	.	-0.30	0.36
	Val	1617	.	.	B	B	.	.	.	1.04	0.30	.	*	.	-0.30	0.46
50	Phe	1618	.	.	B	B	.	.	.	1.16	0.29	*	.	.	-0.30	0.34
	Cys	1619	.	.	B	B	.	.	.	1.19	0.29	*	.	.	0.04	0.39
	Gln	1620	.	.	B	B	.	.	.	0.73	-0.11	*	*	.	0.98	0.87
	Thr	1621	T	T	.	-0.16	-0.33	*	*	F	2.27	0.99
	Arg	1622	T	T	.	0.39	-0.43	*	*	F	2.76	1.30
55	Asp	1623	T	T	.	0.28	-0.51	.	*	F	3.40	1.08
	Gly	1624	T	T	.	0.73	-0.23	.	*	F	2.61	0.62
	Ile	1625	T	.	.	0.43	-0.29	*	*	F	2.07	0.49
	Thr	1626	C	0.74	0.10	*	*	F	1.21	0.39
	Leu	1627	.	.	B	.	.	T	.	0.63	0.10	*	*	F	1.15	0.69
60	Pro	1628	.	.	B	.	.	T	.	-0.03	0.07	.	.	F	1.24	1.70
	Ser	1629	T	T	.	0.01	-0.04	.	.	F	2.37	0.63
	Glu	1630	T	T	.	0.31	-0.14	.	.	F	2.80	1.02
	Gln	1631	T	.	.	-0.19	-0.33	.	.	F	2.17	0.67
	Cys	1632	T	.	.	0.41	-0.07	*	*	.	1.74	0.41
60	Ser	1633	.	.	B	0.73	-0.03	*	*	.	1.06	0.37
	Ala	1634	.	.	B	0.82	-0.03	*	.	.	0.78	0.42
	Leu	1635	.	.	B	.	.	T	.	-0.03	0.00	*	.	.	0.25	1.20

	Pro	1636	T	C	-0.33	0.07	*	.	F	0.61	0.66
	Arg	1637	.	.	B	.	T	.	0.02	0.07	*	.	F	0.57	0.88
	Pro	1638	T	T	0.32	0.06	*	.	F	1.28	1.54
5	Val	1639	T	.	0.91	-0.23	*	.	F	1.84	1.73
	Ser	1640	.	.	B	.	.	.	1.06	-0.26	*	.	F	1.60	1.42
	Thr	1641	.	.	B	.	T	.	0.98	0.31	.	.	F	0.89	0.49
	Gln	1642	T	T	0.57	0.80	.	.	F	0.83	0.70
	Asn	1643	T	T	0.78	0.54	.	.	F	0.67	0.70
10	Cys	1644	T	T	1.04	0.16	.	.	.	0.66	0.84
	Trp	1645	.	A	.	.	T	.	0.68	0.17	*	.	.	0.10	0.49
	Ser	1646	.	A	.	.	.	C	0.69	0.34	*	.	.	-0.10	0.16
	Glu	1647	.	A	.	.	T	.	-0.17	0.33	.	.	.	0.10	0.41
	Ala	1648	.	A	.	B	T	.	-0.20	0.40	.	.	.	-0.20	0.29
	Cys	1649	.	A	.	B	T	.	0.18	-0.01	*	*	.	0.70	0.29
15	Ser	1650	.	.	.	B	T	.	0.58	0.51	*	*	.	-0.20	0.18
	Val	1651	.	.	B	B	.	.	0.02	0.51	*	*	.	-0.60	0.34
	His	1652	.	.	.	B	T	.	-0.28	0.66	.	*	.	-0.20	0.47
	Trp	1653	.	.	B	B	.	.	-0.50	0.47	.	*	.	-0.60	0.47
20	Arg	1654	.	.	B	B	.	.	-0.12	0.77	.	*	.	-0.60	0.53
	Val	1655	.	.	B	B	.	.	-0.13	1.04	.	*	.	-0.60	0.41
	Ser	1656	.	.	.	B	T	.	-0.09	1.03	.	*	.	-0.20	0.56
	Leu	1657	.	.	.	B	T	.	-0.72	0.80	.	*	.	-0.20	0.24
	Trp	1658	.	.	.	B	T	.	-0.74	1.37	.	*	.	-0.20	0.17
25	Thr	1659	.	.	B	B	.	.	-1.44	1.21	.	*	.	-0.60	0.18
	Leu	1660	.	.	B	B	.	.	-0.90	1.33	.	.	.	-0.60	0.22
	Cys	1661	.	.	B	B	.	.	-1.27	1.13	.	.	.	-0.60	0.31
	Thr	1662	.	.	B	B	.	.	-0.80	0.79	.	.	.	-0.60	0.11
	Ala	1663	.	.	B	B	.	.	-0.51	0.73	.	.	.	-0.60	0.14
30	Thr	1664	.	.	.	B	T	.	-0.44	0.44	.	.	.	-0.20	0.41
	Cys	1665	T	T	0.02	0.63	.	.	.	0.20	0.45
	Gly	1666	T	T	-0.01	0.57	.	.	.	0.20	0.44
	Asn	1667	T	T	0.30	0.86	.	.	.	0.20	0.26
	Tyr	1668	T	T	0.59	0.77	.	*	.	0.20	0.85
35	Gly	1669	T	.	1.01	0.59	.	*	.	0.41	1.15
	Phe	1670	T	.	1.79	0.16	*	.	.	0.97	1.40
	Gln	1671	.	.	B	.	.	T	1.28	-0.24	.	*	F	1.78	1.75
	Ser	1672	.	.	B	.	.	T	1.28	-0.36	.	*	F	2.04	1.31
	Arg	1673	.	.	B	.	.	T	0.86	-0.79	.	.	F	2.60	2.62
40	Arg	1674	.	.	B	.	.	T	0.34	-1.00	.	.	F	2.19	0.81
	Val	1675	.	A	B	.	.	.	1.01	-0.76	.	.	.	1.38	0.45
	Glu	1676	.	A	B	.	.	.	0.42	-0.64	*	.	.	1.12	0.31
	Cys	1677	.	A	B	.	.	.	0.83	-0.14	*	*	.	0.56	0.16
	Val	1678	.	A	B	.	.	.	0.41	-0.14	*	*	.	0.64	0.43
45	His	1679	.	A	B	.	.	.	0.30	-0.30	*	*	.	0.98	0.35
	Ala	1680	.	A	.	.	T	.	1.20	0.10	*	.	.	1.27	1.06
	Arg	1681	T	T	0.61	-0.47	*	*	F	2.76	2.86
	Thr	1682	T	T	0.42	-0.61	*	*	F	3.40	2.13
	Asn	1683	T	T	1.07	-0.47	*	*	F	2.76	1.56
50	Lys	1684	T	T	1.10	-0.54	*	*	F	2.72	1.23
	Ala	1685	.	A	.	.	.	C	1.66	-0.54	*	.	F	1.78	1.48
	Val	1686	.	A	B	.	.	.	0.73	-0.53	*	.	F	1.24	1.25
	Pro	1687	.	A	B	.	.	.	0.38	-0.24	*	.	F	0.45	0.52
	Glu	1688	.	A	B	.	.	.	0.08	0.33	*	.	.	-0.30	0.27
55	His	1689	.	A	B	.	.	.	-0.26	0.21	*	.	.	-0.30	0.49
	Leu	1690	.	A	B	.	.	.	-0.01	0.49	*	.	.	-0.60	0.34
	Cys	1691	T	T	0.63	0.49	*	*	.	0.20	0.19
	Ser	1692	T	T	0.96	0.91	*	.	.	0.20	0.22
	Trp	1693	T	T	0.74	0.41	*	.	.	0.20	0.52
60	Gly	1694	T	0.19	0.16	*	.	.	0.45	1.50
	Pro	1695	C	1.00	0.09	*	.	F	0.40	1.13
	Arg	1696	C	1.38	0.10	.	.	F	0.40	1.73
	Pro	1697	T	T	1.68	0.10	*	.	F	0.80	1.83
	Ala	1698	T	T	2.08	0.07	*	.	F	0.80	2.05

	Asn	1699	T	T	.	1.76	-0.36	.	.	.	1.25	2.05
	Trp	1700	T	T	.	1.97	0.21	.	*	.	0.50	0.71
	Gln	1701	T	T	.	0.97	0.19	.	*	.	0.65	1.13
	Arg	1702	T	T	.	0.87	0.37	.	*	.	0.50	0.49
5	Cys	1703	T	T	.	1.24	0.46	.	*	.	0.45	0.68
	Asn	1704	T	T	.	0.58	-0.03	*	.	.	1.60	0.61
	Ile	1705	C	0.87	0.14	.	*	F	1.00	0.17
	Thr	1706	T	C	0.87	0.14	.	*	F	1.45	0.54
	Pro	1707	T	T	.	0.16	-0.03	*	*	F	2.50	0.54
10	Cys	1708	T	T	.	0.82	0.19	.	*	F	1.65	0.76
	Glu	1709	T	T	.	0.16	-0.50	*	*	F	2.00	0.91
	Asn	1710	T	.	.	1.16	-0.41	.	*	.	1.74	0.31
	Met	1711	T	.	.	1.47	-0.84	.	*	.	2.28	1.15
	Glu	1712	T	.	.	1.37	-1.41	.	*	.	2.37	1.11
15	Cys	1713	T	T	.	1.72	-0.93	*	*	.	2.76	0.99
	Arg	1714	T	T	.	1.83	-0.84	*	*	F	3.40	1.45
	Asp	1715	T	T	.	1.59	-1.46	*	*	F	3.06	1.64
	Thr	1716	T	T	.	1.52	-0.70	*	*	F	2.72	4.79
	Thr	1717	.	A	.	.	T	.	.	1.52	-0.70	*	*	F	1.98	1.31
20	Arg	1718	.	A	.	.	T	.	.	2.23	-0.70	*	*	F	1.64	1.36
	Tyr	1719	.	A	.	.	T	.	.	1.27	-0.70	*	*	.	1.15	1.88
	Cys	1720	.	A	B	1.31	-0.54	*	*	.	0.60	0.97
	Glu	1721	.	A	B	1.62	-1.03	*	*	.	0.60	0.99
25	Lys	1722	.	A	B	.	T	.	.	1.12	-0.63	*	*	F	1.30	1.09
	Val	1723	.	A	.	.	T	.	.	1.06	-0.70	*	*	F	1.30	1.68
	Lys	1724	.	A	B	.	T	.	.	0.49	-1.27	.	.	F	1.30	1.94
	Gln	1725	.	A	B	0.49	-0.59	.	.	F	0.75	0.80
	Leu	1726	.	A	B	0.49	-0.01	.	.	F	0.45	0.58
	Lys	1727	.	A	B	-0.37	-0.26	.	.	.	0.30	0.50
30	Leu	1728	.	A	B	B	.	.	.	0.19	0.43	.	.	.	-0.60	0.24
	Cys	1729	.	A	B	B	.	.	.	0.14	0.41	.	.	.	-0.60	0.39
	Gln	1730	.	A	B	B	.	.	.	-0.56	0.13	.	*	.	-0.30	0.34
	Leu	1731	.	A	B	B	.	.	.	0.30	0.91	.	*	.	-0.60	0.35
	Ser	1732	.	A	.	.	T	.	.	-0.04	0.23	*	*	.	0.25	1.32
35	Gln	1733	.	A	.	.	T	.	.	0.88	0.04	*	*	F	0.40	1.02
	Phe	1734	.	A	.	.	T	.	.	0.88	-0.36	*	*	F	1.28	2.42
	Lys	1735	.	A	.	.	T	.	.	0.21	-0.47	*	*	F	1.41	0.97
	Ser	1736	T	T	.	0.68	-0.29	.	*	F	2.09	0.30
	Arg	1737	T	T	.	0.67	-0.26	.	*	F	2.37	0.34
40	Cys	1738	T	T	.	0.00	-0.56	.	*	.	2.80	0.25
	Cys	1739	T	T	.	0.36	0.01	.	*	.	1.62	0.10
	Gly	1740	T	T	.	0.36	0.06	*	*	.	1.34	0.05
	Thr	1741	T	T	.	0.07	0.06	*	*	F	1.21	0.19
	Cys	1742	T	T	.	-0.43	-0.01	*	*	F	1.66	0.35
45	Gly	1743	T	T	.	-0.16	-0.16	.	.	F	1.51	0.45
	Lys	1744	.	.	B	0.12	-0.16	.	.	.	0.89	0.40
	Ala	1745	.	.	B	0.08	-0.21	.	.	.	1.02	0.96

Table 8

	Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
5	Ala	1	.	.	B	0.06	-0.10	*	.	.	0.50	0.80
	Ile	2	.	.	B	0.44	-0.04	*	.	.	0.50	0.91
	Arg	3	.	.	B	0.83	-0.47	*	*	.	0.65	1.23
	Pro	4	.	.	B	0.88	-0.90	*	*	.	0.95	2.11
	Thr	5	A	0.92	-0.97	*	*	F	1.10	2.97
10	Glu	6	A	T	.	0.70	-1.23	*	*	F	1.30	1.50
	Glu	7	A	T	.	1.56	-0.54	*	*	F	1.15	0.80
	Gly	8	A	T	.	0.59	-0.47	*	*	F	0.85	0.76
	Gly	9	A	T	.	0.77	-0.31	.	*	F	0.85	0.32
	Leu	10	A	.	.	B	.	.	.	0.48	0.19	.	*	.	-0.30	0.25
15	His	11	A	.	.	B	.	.	.	0.48	0.80	.	*	.	-0.60	0.25
	Val	12	A	.	.	B	.	.	.	-0.22	0.37	.	*	.	-0.30	0.45
	His	13	.	.	B	B	.	.	.	-0.09	0.73	.	*	.	-0.60	0.47
	Met	14	.	.	B	-0.09	0.47	.	*	.	-0.15	0.53
	Glu	15	.	.	B	0.13	0.40	.	*	.	0.10	0.71
20	Phe	16	.	.	B	0.17	0.26	.	*	.	0.65	0.53
	Pro	17	T	.	.	0.68	-0.24	.	*	F	2.05	0.89
	Gly	18	T	T	.	0.04	-0.43	.	.	F	2.50	0.51
	Ala	19	T	T	.	0.64	0.14	.	.	F	1.65	0.31
	Asp	20	T	T	.	0.64	-0.24	.	.	F	2.00	0.33
25	Gly	21	T	T	.	0.49	-0.27	.	.	F	1.75	0.57
	Cys	22	T	.	.	0.70	-0.06	.	*	F	1.30	0.42
	Asn	23	.	.	B	0.46	-0.56	.	*	F	0.95	0.42
	Gln	24	.	A	B	1.04	-0.06	.	*	.	0.30	0.43
	Val	25	.	A	B	0.80	-0.49	.	*	.	0.45	1.38
30	Asp	26	A	A	0.33	-0.30	.	.	.	0.45	1.35
	Ala	27	A	A	1.04	-0.01	*	.	.	0.30	0.64
	Glu	28	A	A	0.19	-0.41	*	.	.	0.45	1.73
	Tyr	29	A	A	.	B	.	.	.	-0.16	-0.41	*	.	.	0.30	0.77
	Leu	30	A	A	.	B	.	.	.	0.40	0.01	.	.	.	-0.30	0.75
35	Lys	31	A	A	.	B	.	.	.	0.40	-0.10	.	.	F	0.45	0.58
	Val	32	A	A	.	B	.	.	.	0.64	-0.10	*	*	F	0.73	0.64
	Gly	33	A	T	.	0.61	-0.43	.	*	F	1.41	0.77
	Ser	34	A	T	.	0.16	-0.61	*	*	F	1.99	0.53
	Glu	35	A	T	.	1.08	0.17	*	*	F	1.37	0.61
40	Gly	36	T	T	.	0.18	-0.47	*	*	F	2.80	1.22
	His	37	.	.	B	0.82	-0.26	.	*	.	1.62	0.67
	Phe	38	.	.	B	0.58	-0.21	.	*	.	1.34	0.60
	Arg	39	.	.	B	0.07	0.29	.	*	.	0.46	0.61
	Val	40	.	.	B	-0.28	0.54	.	*	.	-0.12	0.37
45	Pro	41	.	.	B	-0.18	0.47	.	*	.	-0.40	0.42
	Ala	42	.	.	.	B	T	.	.	-0.96	0.44	.	*	.	-0.20	0.34
	Leu	43	.	.	B	B	.	.	.	-0.26	1.13	.	*	.	-0.60	0.38
	Gly	44	.	.	B	B	.	.	.	-1.22	0.49	*	*	.	-0.60	0.41
	Tyr	45	.	.	B	B	.	.	.	-0.26	0.70	*	*	.	-0.60	0.30
50	Leu	46	.	.	B	B	.	.	.	-0.93	0.20	.	*	.	-0.30	0.71
	Asp	47	.	.	B	B	.	.	.	-1.20	0.20	*	*	.	-0.30	0.50
	Val	48	.	.	B	B	.	.	.	-0.39	0.41	*	*	.	-0.60	0.24
	Arg	49	.	.	B	B	.	.	.	-0.36	-0.34	.	*	.	0.30	0.48
	Ile	50	.	.	B	B	.	.	.	-0.11	-0.54	.	*	.	0.88	0.42
55	Val	51	.	.	B	B	.	.	.	0.46	-0.54	.	*	.	1.16	0.94
	Asp	52	.	.	B	.	.	T	.	0.16	-0.43	*	*	F	1.69	0.75
	Thr	53	.	.	B	.	.	T	.	0.71	-0.04	*	.	F	2.12	1.44
	Asp	54	T	T	.	-0.10	-0.34	*	.	F	2.80	2.60
	Tyr	55	T	T	.	0.20	-0.20	.	.	F	2.52	1.35
60	Ser	56	.	.	.	B	.	.	C	0.20	0.30	.	.	F	0.89	0.94
	Ser	57	.	.	B	B	.	.	.	-0.61	0.46	.	.	.	-0.04	0.42
	Phe	58	.	.	B	B	.	.	.	-0.54	1.14	.	.	.	-0.32	0.22
	Ala	59	.	.	B	B	.	.	.	-1.43	1.14	.	.	.	-0.60	0.26
	Val	60	.	.	B	B	.	.	.	-1.43	1.44	.	.	.	-0.60	0.13

5	Leu	61	.	.	B	B	.	.	.	-1.09	1.81	.	.	.	-0.60	0.24
	Tyr	62	.	.	B	B	.	.	.	-0.79	1.03	.	.	.	-0.60	0.48
	Ile	63	.	.	B	B	.	.	.	-0.90	0.53	*	.	.	-0.45	1.13
	Tyr	64	A	A	-0.31	0.57	*	.	.	-0.45	1.13
	Lys	65	A	A	0.20	-0.11	*	.	.	0.45	1.25
10	Glu	66	A	A	0.42	-0.44	*	*	F	0.60	1.76
	Leu	67	A	A	-0.14	-0.63	*	.	F	0.90	1.13
	Glu	68	A	A	0.44	-0.70	*	.	F	0.75	0.47
	Gly	69	A	A	0.38	-0.31	*	.	F	0.45	0.36
	Ala	70	A	A	.	B	.	.	.	-0.27	0.17	*	.	.	-0.30	0.63
15	Leu	71	A	A	.	B	.	.	.	-1.12	0.10	*	*	.	-0.30	0.36
	Ser	72	A	A	.	B	.	.	.	-0.31	0.74	*	*	.	-0.60	0.27
	Thr	73	A	A	.	B	.	.	.	-1.12	0.71	*	*	.	-0.60	0.47
	Met	74	A	A	.	B	.	.	.	-1.02	0.90	*	.	.	-0.60	0.47
	Val	75	.	A	B	B	.	.	.	-0.73	0.97	*	*	.	-0.60	0.54
20	Gln	76	.	A	B	B	.	.	.	0.19	0.97	*	*	.	-0.60	0.50
	Leu	77	.	A	B	B	.	.	.	0.18	0.49	*	*	.	-0.60	1.00
	Tyr	78	.	A	B	B	.	.	.	0.49	0.36	*	*	.	0.19	1.94
	Ser	79	.	.	B	.	.	T	.	1.09	0.11	*	*	F	1.08	1.94
	Arg	80	.	.	B	.	.	T	.	1.09	-0.29	*	*	F	2.02	3.94
25	Thr	81	T	T	.	0.79	-0.33	*	*	F	2.76	1.86
	Gln	82	T	T	.	1.39	-0.70	*	.	F	3.40	1.86
	Asp	83	T	.	.	1.63	-0.66	*	.	F	2.86	1.47
	Val	84	.	.	B	1.34	-0.26	*	.	F	1.82	1.77
	Ser	85	.	.	B	.	.	T	.	0.42	-0.24	*	.	F	1.68	1.03
30	Pro	86	.	.	B	.	.	T	.	0.78	0.04	*	.	F	0.59	0.51
	Gln	87	A	T	.	0.19	0.04	*	.	F	0.40	1.37
	Ala	88	A	T	.	-0.51	-0.10	*	.	.	0.85	1.03
	Leu	89	A	A	0.34	0.30	*	.	.	-0.30	0.58
	Lys	90	.	A	B	0.64	0.27	*	.	.	-0.30	0.58
35	Ala	91	.	A	B	0.16	-0.13	*	.	.	0.30	0.96
	Phe	92	.	A	B	-0.09	0.16	*	.	.	-0.15	1.00
	Gln	93	.	A	B	0.29	0.23	*	.	.	-0.30	0.79
	Asp	94	.	A	B	0.79	0.66	*	*	.	-0.45	1.20
	Phe	95	.	A	B	-0.07	0.64	*	.	.	-0.45	2.01
40	Tyr	96	.	A	B	0.18	0.54	*	.	.	-0.60	0.96
	Pro	97	C	0.07	0.57	*	.	F	-0.05	0.57
	Thr	98	T	.	.	-0.14	1.26	.	.	.	0.00	0.54
	Leu	99	C	-0.14	0.90	.	*	.	-0.20	0.53
	Gly	100	C	0.56	0.14	.	.	.	0.10	0.60
45	Leu	101	.	A	C	0.20	-0.29	.	.	F	0.65	0.69
	Pro	102	A	A	-0.19	-0.16	.	.	F	0.45	0.83
	Glu	103	A	A	-0.73	-0.23	.	.	F	0.45	0.83
	Asp	104	A	A	-0.52	-0.01	.	.	.	0.30	0.75
	Met	105	A	A	-0.99	-0.09	.	.	.	0.30	0.48
50	Met	106	A	A	-0.39	0.17	.	.	.	-0.30	0.23
	Val	107	A	A	-0.18	0.60	.	.	.	-0.60	0.21
	Met	108	A	A	-0.48	1.00	.	.	.	-0.60	0.37
	Leu	109	A	A	-0.48	0.77	.	.	.	-0.60	0.50
	Pro	110	A	A	-0.47	0.16	.	.	F	0.00	1.12
55	Gln	111	A	T	.	-0.53	0.01	.	.	F	0.40	1.14
	Ser	112	A	T	.	0.32	-0.03	.	.	F	0.85	0.74
	Asp	113	A	T	.	0.71	-0.31	.	.	F	0.85	0.77
	Ala	114	T	T	.	1.52	-0.31	.	.	F	1.59	0.69
	Cys	115	C	1.43	-0.71	.	.	.	1.68	0.89
60	Asn	116	T	C	1.48	-0.71	.	.	F	2.37	0.72
	Pro	117	T	C	1.78	-0.71	*	.	F	2.86	1.42
	Glu	118	T	T	.	1.19	-1.21	*	.	F	3.40	4.58
	Ser	119	A	T	.	1.57	-1.29	.	.	F	2.66	2.88
	Lys	120	A	A	1.84	-1.26	.	.	F	1.92	2.88
60	Glu	121	A	A	1.46	-1.26	.	.	.	1.43	2.12
	Ala	122	A	A	1.28	-0.83	.	.	.	1.09	2.03
	Pro	123	A	A	0.89	-0.79	.	.	.	0.75	1.30

Table 9

	Res Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
5	Met 1	A	A	-0.73	0.40	.	.	.	-0.60	0.50
	Ala 2	A	A	-0.93	0.47	.	.	.	-0.60	0.39
	Ser 3	A	A	-1.40	0.54	.	.	.	-0.60	0.31
	Met 4	A	A	-1.82	0.76	.	.	.	-0.60	0.23
10	Ala 5	A	A	-1.74	0.83	.	.	.	-0.60	0.19
	Ala 6	A	A	-1.43	0.81	.	.	.	-0.60	0.20
	Val 7	A	A	-1.43	1.34	.	.	.	-0.60	0.22
	Leu 8	A	A	-1.94	1.23	.	.	.	-0.60	0.22
15	Thr 9	A	A	-1.93	1.41	.	.	.	-0.60	0.18
	Trp 10	A	A	-2.16	1.41	.	.	.	-0.60	0.24
	Ala 11	A	A	-2.38	1.46	.	.	.	-0.60	0.24
	Leu 12	A	A	-1.82	1.46	.	.	.	-0.60	0.14
20	Ala 13	A	A	-1.60	1.36	.	.	.	-0.60	0.18
	Leu 14	A	A	-1.99	0.94	.	.	.	-0.60	0.18
	Leu 15	A	A	-2.00	1.23	.	.	.	-0.60	0.18
	Ser 16	A	A	-2.00	0.93	.	.	.	-0.60	0.24
25	Ala 17	A	A	-1.50	0.93	.	.	.	-0.60	0.30
	Phe 18	A	A	-0.91	0.73	.	.	.	-0.60	0.53
	Ser 19	A	A	-0.69	0.44	.	.	.	-0.60	0.68
	Ala 20	A	A	0.23	0.56	.	.	.	-0.60	0.68
30	Thr 21	A	A	0.58	0.06	.	.	F	0.00	1.53
	Gln 22	A	A	0.82	-0.73	.	.	F	1.18	2.29
	Ala 23	A	A	0.82	-0.69	.	.	F	1.46	2.24
	Arg 24	T	T	.	0.83	-0.40	*	.	F	2.24	1.35
35	Lys 25	T	T	.	1.42	0.03	*	.	F	1.77	0.82
	Gly 26	T	T	.	1.49	-0.37	*	.	F	2.80	1.35
	Phe 27	T	T	.	0.79	-0.11	*	.	.	2.37	1.08
	Trp 28	T	.	.	1.08	0.67	*	.	.	0.84	0.47
40	Asp 29	C	0.97	1.06	.	.	.	0.36	0.63
	Tyr 30	T	.	.	0.61	1.03	*	.	.	0.43	1.27
	Phe 31	T	.	.	0.66	0.73	.	.	.	0.15	1.74
	Ser 32	T	.	.	1.01	0.20	*	.	F	0.94	1.40
45	Gln 33	T	T	.	1.30	0.63	.	.	F	1.03	0.88
	Thr 34	T	T	.	1.34	-0.13	.	.	F	2.42	1.70
	Ser 35	T	C	1.24	-0.91	.	.	F	2.86	2.54
	Gly 36	T	T	.	2.06	-0.87	.	*	F	3.40	1.45
50	Asp 37	T	T	.	1.50	-1.27	.	*	F	3.06	1.97
	Lys 38	T	C	1.50	-1.11	.	*	F	2.52	1.09
	Gly 39	T	C	1.81	-1.50	.	*	F	2.18	1.91
	Arg 40	A	T	.	1.22	-1.53	.	.	F	1.64	1.98
55	Val 41	A	A	1.53	-0.84	.	*	F	0.75	0.69
	Glu 42	A	A	1.53	-0.34	.	*	F	0.45	0.95
	Gln 43	A	A	1.49	-0.37	.	*	.	0.30	0.84
	Ile 44	A	A	1.88	0.03	.	*	.	-0.15	1.97
60	His 45	A	A	1.17	-0.61	.	.	F	0.90	2.27
	Gln 46	A	A	1.43	0.00	.	.	F	0.00	1.30
	Gln 47	A	A	1.54	0.10	.	.	F	0.00	1.87
	Lys 48	A	A	1.54	-0.59	.	.	F	0.90	2.69
55	Met 49	A	A	2.22	-1.09	.	.	F	0.90	2.69
	Ala 50	A	A	1.67	-1.06	*	.	F	0.90	2.40
	Arg 51	A	A	1.36	-0.96	*	.	F	0.90	1.21
	Glu 52	A	A	0.54	-0.47	*	*	F	0.60	1.77
60	Pro 53	A	A	0.54	-0.40	*	.	F	0.60	1.45
	Ala 54	A	A	1.14	-0.90	*	*	F	0.90	1.48
	Thr 55	A	A	1.43	-0.90	*	*	F	0.90	1.42
	Leu 56	A	T	.	0.51	-0.51	*	*	F	1.30	1.23
60	Lys 57	A	T	.	0.51	-0.26	.	.	F	1.00	1.01
	Asp 58	A	T	.	0.72	-0.76	.	*	F	1.30	1.21
	Ser 59	A	T	.	1.31	-0.84	.	*	F	1.30	2.54
	Leu 60	A	A	0.81	-1.53	*	*	F	0.90	2.12

	Glu	61	A	A	1.62	-0.84	*	*	F	0.90	1.05
	Gln	62	A	A	1.58	-0.44	*	*	F	0.60	1.26
	Asp	63	A	A	0.98	-0.43	*	.	F	0.60	2.45
	Lcu	64	A	A	1.28	-0.50	*	.	F	0.60	1.40
5	Asn	65	A	A	2.13	-0.10	*	.	F	0.60	1.30
	Asn	66	A	T	.	1.43	-0.50	*	.	F	0.85	1.56
	Met	67	A	T	.	0.62	0.29	*	.	.	0.25	1.63
	Asn	68	A	T	.	0.62	0.29	*	.	.	0.10	0.84
10	Lys	69	A	T	.	1.48	-0.11	*	.	.	0.70	0.90
	Phe	70	A	A	0.67	-0.51	*	*	.	0.75	1.82
	Leu	71	A	A	0.78	-0.44	*	*	.	0.30	0.94
	Glu	72	A	A	1.17	-0.84	*	*	F	0.75	0.92
	Lys	73	A	A	0.36	-0.41	*	*	F	0.60	1.64
	Leu	74	A	A	0.01	-0.51	*	*	F	0.90	1.64
15	Arg	75	A	A	0.37	-0.81	*	.	F	0.90	1.27
	Pro	76	.	A	C	0.88	-0.39	.	.	F	0.65	0.63
	Leu	77	T	C	0.88	0.00	.	*	F	0.60	1.02
	Ser	78	T	C	0.24	-0.69	.	*	F	1.35	0.90
20	Gly	79	T	C	0.84	-0.19	.	*	F	1.35	0.59
	Ser	80	T	C	0.84	-0.19	.	*	F	1.80	1.10
	Glu	81	C	0.24	-0.87	.	*	F	2.20	1.61
	Ala	82	C	0.84	-0.57	*	.	F	2.50	1.34
	Pro	83	T	.	.	1.14	-0.57	*	.	F	3.00	1.55
25	Arg	84	T	.	.	1.49	-0.56	*	.	F	2.70	1.55
	Leu	85	C	1.58	-0.56	*	.	F	2.20	2.56
	Pro	86	T	.	.	0.72	-0.63	*	.	F	2.35	2.56
	Gln	87	T	.	.	0.97	-0.41	*	.	F	1.85	0.97
	Asp	88	T	C	0.58	0.01	.	*	F	1.35	1.16
30	Pro	89	T	C	0.58	-0.06	*	.	F	2.05	0.75
	Val	90	T	T	.	1.50	-0.49	.	.	F	2.50	0.84
	Gly	91	T	C	1.71	-0.89	.	.	.	2.20	0.99
	Met	92	A	A	0.90	-0.49	.	*	.	1.20	1.11
	Arg	93	A	A	0.90	-0.23	.	.	.	0.95	1.23
35	Arg	94	A	A	1.11	-0.47	.	*	F	0.85	2.15
	Gln	95	A	A	1.97	-0.90	.	*	F	0.90	3.77
	Leu	96	A	A	1.50	-1.51	*	*	F	0.90	3.33
	Gln	97	A	A	2.10	-0.83	*	*	F	0.90	1.40
	Glu	98	A	A	1.99	-0.83	*	*	F	0.90	1.40
40	Glu	99	A	A	1.02	-1.23	*	.	F	0.90	2.95
	Leu	100	A	A	1.07	-1.27	.	*	F	0.90	1.26
	Glu	101	A	A	1.29	-1.67	.	*	F	0.90	1.46
	Glu	102	A	A	1.40	-1.17	.	*	F	0.75	0.85
	Val	103	A	A	0.59	-1.17	*	*	F	0.90	2.02
45	Lys	104	A	A	0.59	-1.17	.	*	F	0.75	0.96
	Ala	105	A	A	1.19	-0.77	.	*	F	0.60	0.96
	Arg	106	A	A	0.94	-0.34	.	*	.	0.45	2.00
	Leu	107	A	A	0.34	-0.23	.	*	.	0.45	1.57
	Gln	108	A	T	.	0.61	0.39	.	*	.	0.25	1.54
50	Pro	109	A	T	.	0.57	0.39	.	*	.	0.10	0.79
	Tyr	110	A	T	.	0.57	0.39	.	*	.	0.25	1.67
	Met	111	A	T	.	0.42	0.20	*	*	.	0.10	0.97
	Ala	112	A	A	1.23	0.30	.	.	.	-0.30	0.85
	Glu	113	A	A	0.42	-0.13	.	.	.	0.30	0.94
55	Ala	114	A	A	-0.22	-0.20	.	.	.	0.30	0.79
	His	115	A	A	-0.32	-0.17	.	.	.	0.30	0.58
	Glu	116	A	A	-0.01	-0.24	.	.	.	0.30	0.33
	Leu	117	A	A	0.58	0.67	.	.	.	-0.60	0.34
	Val	118	A	A	-0.23	0.57	.	.	.	-0.60	0.41
60	Gly	119	A	A	0.36	0.76	.	*	.	-0.60	0.19
	Trp	120	A	A	0.04	0.76	.	.	.	-0.60	0.41
	Asn	121	A	A	-0.77	0.50	*	.	.	-0.60	0.54
	Leu	122	A	A	0.16	0.54	*	.	.	-0.60	0.45
	Glu	123	A	A	1.01	0.11	.	*	.	-0.30	0.84

5	Gly	124	A	A	1.36	-0.40	.	*	F	0.45	0.91
	Leu	125	A	A	0.83	-0.40	*	*	F	0.60	1.90
	Arg	126	A	A	0.88	-0.40	*	*	F	0.45	0.91
	Gln	127	A	A	1.48	-0.40	*	*	F	0.60	1.83
	Gln	128	.	A	.	.	T	.	1.23	-0.40	*	*	F	1.25	3.43
10	Leu	129	.	A	.	.	.	C	1.27	-0.33	*	*	F	1.30	2.75
	Lys	130	T	C	1.48	0.16	.	*	F	1.35	2.29
	Pro	131	T	C	1.37	0.37	.	*	F	1.60	1.31
	Tyr	132	T	.	0.56	-0.03	.	.	.	2.50	2.65
	Thr	133	A	.	.	.	T	.	-0.04	-0.03	.	.	.	1.85	1.09
15	Met	134	A	A	0.77	0.59	.	.	.	0.15	0.70
	Asp	135	A	A	0.72	0.16	.	.	.	0.20	0.77
	Leu	136	A	A	0.08	-0.20	*	.	.	0.55	0.93
	Met	137	A	A	-0.27	-0.04	.	*	.	0.30	0.70
	Glu	138	A	A	-0.77	-0.16	*	*	.	0.30	0.42
20	Gln	139	A	A	-0.06	0.53	*	*	.	-0.60	0.42
	Val	140	A	A	-0.91	-0.16	*	*	.	0.30	0.83
	Ala	141	A	A	-0.10	-0.13	*	*	.	0.30	0.36
	Leu	142	A	A	0.50	0.27	*	*	.	-0.30	0.36
	Arg	143	A	A	-0.31	-0.13	.	*	.	0.30	0.83
25	Val	144	A	A	-0.31	-0.09	.	*	.	0.30	0.68
	Gln	145	A	A	0.54	-0.19	.	*	.	0.45	1.43
	Glu	146	A	A	1.13	-0.87	*	*	F	0.90	1.26
	Leu	147	A	A	1.13	-0.47	.	*	F	0.60	2.95
	Gln	148	A	A	1.13	-0.43	.	*	F	0.60	1.40
30	Glu	149	A	A	1.13	-0.83	*	*	F	0.90	1.59
	Gln	150	A	A	0.28	-0.19	*	*	F	0.60	1.43
	Leu	151	A	A	-0.07	-0.23	*	*	.	0.30	0.61
	Arg	152	A	A	0.74	-0.20	*	*	.	0.30	0.35
	Val	153	A	A	0.74	-0.20	*	*	.	0.30	0.35
35	Val	154	A	A	0.43	-0.60	*	*	.	0.60	0.71
	Gly	155	A	.	.	.	T	.	0.48	-0.80	*	*	F	1.15	0.52
	Glu	156	A	.	.	.	T	.	0.70	-0.80	*	*	F	1.30	1.41
	Asp	157	A	.	.	.	T	.	0.59	-0.94	.	*	F	1.30	1.91
	Thr	158	A	.	.	.	T	.	0.63	-1.19	.	.	F	1.30	3.35
40	Lys	159	A	A	0.68	-0.93	.	*	F	0.90	1.59
	Ala	160	A	A	0.68	-0.24	.	.	F	0.45	0.79
	Gln	161	A	A	0.33	0.19	.	*	.	-0.30	0.54
	Leu	162	A	A	-0.52	0.13	.	*	.	-0.30	0.27
	Leu	163	A	A	-0.21	0.77	.	*	.	-0.60	0.20
45	Gly	164	.	A	.	.	.	C	-0.26	0.27	.	*	F	0.05	0.19
	Gly	165	.	A	.	.	.	C	-0.26	-0.13	*	.	F	0.65	0.40
	Val	166	A	A	-0.54	-0.31	*	.	F	0.45	0.49
	Asp	167	A	A	-0.32	-0.09	.	.	F	0.45	0.52
	Glu	168	A	A	-0.32	-0.01	.	.	.	0.30	0.53
50	Ala	169	A	A	-0.79	0.24	.	.	.	-0.30	0.59
	Trp	170	A	A	-0.44	0.29	.	.	.	-0.30	0.29
	Ala	171	A	A	0.07	0.69	*	.	.	-0.60	0.29
	Leu	172	A	A	-0.74	1.11	*	.	.	-0.60	0.28
	Leu	173	A	A	-0.74	1.30	.	.	.	-0.60	0.22
55	Gln	174	A	A	-0.46	0.79	.	.	.	-0.60	0.38
	Gly	175	A	A	-0.06	0.67	.	*	F	-0.45	0.62
	Leu	176	A	A	-0.32	-0.01	.	.	F	0.60	1.47
	Gln	177	A	A	-0.37	-0.06	.	.	F	0.45	0.63
	Ser	178	A	A	0.41	0.19	.	.	F	-0.15	0.47
60	Arg	179	.	.	B	B	.	.	0.38	0.26	.	.	F	-0.15	0.78
	Val	180	.	.	B	B	.	.	0.41	0.07	.	*	.	-0.30	0.61
	Val	181	.	.	B	B	.	.	0.88	0.16	*	*	.	-0.30	0.66
	His	182	.	.	.	B	.	.	0.99	0.20	*	*	.	-0.10	0.33
	His	183	T	C	0.59	0.20	*	*	.	0.30	0.88
60	Thr	184	T	C	0.52	0.34	*	*	F	0.60	1.03
	Gly	185	T	C	1.38	-0.30	*	*	F	1.20	1.51
	Arg	186	A	.	.	.	T	.	1.42	-0.80	*	*	F	1.30	1.92

	Phe	187	A	A	0.76	-0.61	*	*	F	0.90	1.10
	Lys	188	A	A	0.76	-0.31	.	*	F	0.45	0.96
	Glu	189	A	A	0.86	-0.24	*	*	.	0.30	0.67
	Leu	190	A	A	0.96	0.19	*	*	.	-0.15	1.19
5	Phe	191	A	A	0.26	0.16	*	*	.	-0.30	0.93
	His	192	A	T	0.96	0.66	*	.	.	-0.20	0.55
	Pro	193	A	T	0.61	0.66	*	.	.	-0.05	1.14
	Tyr	194	A	T	-0.20	0.36	*	.	.	0.25	1.77
10	Ala	195	A	T	-0.24	0.26	*	.	.	0.25	1.07
	Glu	196	A	0.16	0.40	*	.	.	-0.40	0.52
	Ser	197	A	-0.16	0.36	*	.	.	-0.10	0.44
	Leu	198	A	-0.83	0.03	*	.	.	-0.10	0.43
	Val	199	A	-0.93	0.21	*	.	.	-0.10	0.17
	Ser	200	A	-0.23	0.64	*	.	F	-0.25	0.13
15	Gly	201	T	.	-0.27	0.26	*	.	F	0.45	0.31
	Ile	202	A	-0.82	0.07	*	.	F	0.05	0.56
	Gly	203	C	-0.01	0.07	*	.	F	0.25	0.31
	Arg	204	C	0.84	0.09	*	.	F	0.25	0.54
	His	205	A	0.33	-0.34	*	.	.	0.65	1.35
20	Val	206	A	0.64	-0.34	*	.	.	0.65	1.12
	Gln	207	A	1.64	-0.27	*	.	.	0.50	0.78
	Glu	208	A	1.69	-0.27	*	.	.	0.65	1.12
	Leu	209	A	0.72	-0.39	*	.	.	0.65	2.03
	His	210	A	0.17	-0.39	*	.	.	0.50	0.87
25	Arg	211	T	.	0.81	-0.29	*	.	.	0.90	0.51
	Ser	212	T	.	0.78	0.14	*	.	.	0.30	0.95
	Val	213	A	0.19	-0.04	*	.	.	0.50	0.95
	Ala	214	C	0.79	-0.04	*	.	.	0.70	0.49
30	Pro	215	C	0.23	0.39	.	.	.	0.10	0.56
	His	216	C	-0.18	0.50	.	.	.	-0.20	0.77
	Ala	217	C	-0.09	0.24	.	.	.	0.25	1.02
	Pro	218	C	0.18	0.17	.	.	.	0.25	1.02
	Ala	219	C	0.88	0.24	*	*	F	0.25	0.76
	Ser	220	A	T	0.28	-0.26	.	*	F	1.00	1.47
35	Pro	221	A	T	0.01	-0.07	*	.	F	0.85	0.78
	Ala	222	A	T	0.71	-0.11	*	.	F	1.00	1.04
	Arg	223	A	T	0.26	-0.61	*	.	.	1.15	1.52
	Leu	224	A	T	-0.01	-0.43	*	.	.	0.70	0.53
	Ser	225	A	T	0.29	-0.21	*	*	.	0.70	0.39
40	Arg	226	A	T	-0.36	-0.31	*	*	.	0.70	0.34
	Cys	227	A	T	.	-0.58	0.33	*	*	.	0.10	0.31
	Val	228	A	A	.	B	.	.	.	-0.99	0.33	*	*	.	-0.30	0.19
	Gln	229	A	A	.	B	.	.	.	-0.07	0.33	*	.	.	-0.30	0.13
45	Val	230	A	A	.	B	.	.	.	0.28	0.33	*	.	.	-0.30	0.47
	Leu	231	A	A	.	B	.	.	.	-0.64	-0.24	*	.	.	0.45	1.28
	Ser	232	A	A	.	B	.	.	.	-0.29	-0.20	*	.	F	0.45	0.61
	Arg	233	A	A	-0.24	-0.11	.	*	F	0.60	1.18
	Lys	234	A	A	-0.20	-0.07	.	*	F	0.60	1.18
50	Leu	235	A	A	0.07	-0.76	.	*	F	0.90	1.76
	Thr	236	A	A	0.92	-0.64	*	*	.	0.60	0.91
	Leu	237	A	A	0.63	-0.64	*	*	.	0.60	0.91
	Lys	238	A	A	-0.29	-0.14	*	*	F	0.60	1.11
	Ala	239	A	A	-0.37	-0.14	.	*	F	0.45	0.64
	Lys	240	A	A	-0.14	-0.13	.	*	F	0.60	1.05
55	Ala	241	A	A	0.28	-0.31	.	*	.	0.30	0.53
	Leu	242	A	A	0.20	-0.31	.	*	.	0.45	1.03
	His	243	A	A	0.16	-0.13	.	*	.	0.30	0.36
	Ala	244	A	A	0.74	0.27	.	*	.	-0.30	0.62
	Arg	245	A	A	0.70	0.17	.	*	.	-0.15	1.30
60	Ile	246	A	A	0.48	-0.11	*	*	.	0.45	1.53
	Gln	247	A	A	1.29	0.07	*	*	F	0.00	1.25
	Gln	248	A	A	1.32	-0.43	*	*	F	0.60	1.07
	Asn	249	.	A	C	1.10	-0.03	*	*	F	0.80	2.64

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5	Leu	250	.	A	C	1.10	-0.03	*	*	F	0.80	1.26
	Asp	251	.	A	C	1.99	-0.43	*	*	F	0.80	1.42
	Gln	252	.	A	C	1.99	-0.83	*	*	F	1.10	1.53
	Leu	253	A	A	1.18	-1.23	*	.	F	0.90	3.21
	Arg	254	A	A	0.29	-1.23	*	.	F	0.90	1.59
10	Glu	255	A	A	1.21	-0.54	*	.	F	0.75	0.64
	Glu	256	A	A	0.62	-0.94	*	.	F	0.90	1.52
	Leu	257	A	A	-0.08	-1.13	*	*	.	0.60	0.79
	Ile	258	A	A	0.14	-0.34	*	.	.	0.30	0.39
	Arg	259	A	A	-0.31	0.16	.	.	.	-0.30	0.23
15	Ala	260	A	A	-0.62	0.59	*	.	.	-0.60	0.28
	Phe	261	A	A	-0.97	0.39	*	.	.	-0.30	0.57
	Ala	262	A	A	-0.47	0.13	*	.	.	0.00	0.29
	Gly	263	T	C	0.42	0.61	*	*	F	0.75	0.41
	Thr	264	T	C	0.31	0.11	.	.	F	1.35	0.82
20	Gly	265	T	C	0.56	-0.67	.	.	F	2.70	1.40
	Thr	266	T	C	0.67	-0.74	.	.	F	3.00	1.40
	Glu	267	C	0.91	-0.67	.	.	F	2.35	0.98
	Glu	268	T	.	.	1.04	-0.73	.	.	F	2.49	0.98
	Gly	269	T	.	.	1.36	-0.73	.	.	F	2.58	1.05
25	Ala	270	C	1.49	-1.21	.	.	F	2.32	1.01
	Gly	271	T	C	1.80	-0.79	.	.	F	2.31	0.91
	Pro	272	T	C	1.20	-0.39	.	.	F	2.40	1.58
	Asp	273	T	C	0.39	-0.20	.	.	F	2.16	1.55
	Pro	274	A	T	.	0.43	-0.01	.	.	F	1.72	1.29
30	Gln	275	A	A	1.02	-0.06	.	.	.	0.93	1.12
	Met	276	A	A	1.37	-0.49	.	.	.	0.69	1.16
	Leu	277	A	A	0.72	-0.49	*	*	.	0.45	1.30
	Ser	278	A	A	0.83	-0.27	*	*	F	0.45	0.56
	Glu	279	A	A	1.04	-0.67	.	*	F	0.90	1.10
35	Glu	280	A	A	1.16	-0.89	.	*	F	0.90	2.32
	Val	281	A	A	0.94	-1.57	*	*	F	0.90	3.39
	Arg	282	A	A	1.76	-1.27	*	*	F	0.90	1.61
	Gln	283	A	A	1.47	-0.87	*	*	F	0.90	1.61
	Arg	284	A	A	0.77	-0.37	*	*	F	0.60	2.20
40	Leu	285	A	A	0.88	-0.23	*	*	.	0.30	0.97
	Gln	286	A	A	1.73	-0.23	*	*	.	0.73	1.10
	Ala	287	A	A	1.62	-0.23	.	*	.	0.86	0.97
	Phe	288	.	A	.	.	T	.	.	1.31	-0.23	.	.	.	1.69	1.97
	Arg	289	T	T	.	0.96	-0.43	.	*	F	2.52	1.64
45	Gln	290	T	T	.	0.96	-0.07	.	*	F	2.80	2.54
	Asp	291	T	T	.	0.96	0.11	.	*	F	1.92	2.42
	Thr	292	T	T	.	0.66	-0.27	.	*	F	2.24	2.14
	Tyr	293	A	A	0.77	0.41	.	*	.	-0.04	0.87
	Leu	294	A	A	0.07	0.51	.	*	.	-0.32	0.52
50	Gln	295	A	A	-0.63	1.01	.	.	.	-0.60	0.37
	Ile	296	A	A	-0.94	1.31	.	*	.	-0.60	0.20
	Ala	297	A	A	-0.52	1.04	.	*	.	-0.60	0.35
	Ala	298	A	A	-0.87	0.36	*	*	.	-0.30	0.40
	Phe	299	A	A	-0.94	0.46	*	*	.	-0.60	0.58
55	Thr	300	A	A	-0.94	0.46	*	.	.	-0.60	0.40
	Arg	301	A	A	-0.06	-0.04	*	.	.	0.30	0.66
	Ala	302	A	A	0.53	-0.14	*	.	.	0.45	1.33
	Ile	303	A	A	0.81	-0.93	*	.	F	0.90	1.59
	Asp	304	A	A	1.51	-0.93	*	.	F	0.90	1.17
60	Gln	305	A	A	1.82	-0.93	*	.	F	0.90	2.01
	Glu	306	A	A	0.86	-1.43	*	.	F	0.90	4.97
	Thr	307	A	A	1.44	-1.47	*	.	F	0.90	2.21
	Glu	308	A	A	2.33	-1.07	*	.	F	0.90	2.21
	Glu	309	A	A	2.33	-1.07	*	.	F	0.90	2.21
	Val	310	A	A	1.52	-0.67	*	.	F	0.90	2.65
	Gln	311	A	A	0.93	-0.47	.	.	F	0.60	1.26
	Gln	312	A	A	1.03	0.03	.	.	F	-0.15	0.74

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	Gln	313	.	A	.	.	T	.	.	0.82	0.46	.	.	F	0.10	1.53
	Leu	314	.	A	C	0.61	0.24	.	.	F	0.20	1.37
	Ala	315	.	A	C	1.26	0.27	.	.	F	0.20	1.22
	Pro	316	.	A	C	0.91	0.30	.	.	F	0.20	1.09
5	Pro	317	C	0.88	0.33	.	.	F	0.40	1.31
	Pro	318	T	C	0.58	0.14	.	.	F	0.60	1.76
	Pro	319	T	T	.	0.80	0.03	.	.	F	0.80	1.53
	Gly	320	T	T	.	0.69	0.10	.	.	F	0.65	1.00
10	His	321	T	C	0.31	0.46	.	.	.	0.00	0.56
	Ser	322	.	A	C	0.31	0.53	.	.	.	-0.40	0.37
	Ala	323	.	A	C	0.52	0.53	.	.	.	-0.40	0.57
	Phe	324	.	A	C	0.03	0.10	.	.	.	-0.10	0.73
	Ala	325	A	A	0.38	0.39	.	.	.	-0.30	0.47
15	Pro	326	A	A	0.41	0.40	.	.	.	-0.30	0.81
	Glu	327	A	A	0.40	0.30	.	.	F	0.00	1.61
	Phe	328	A	A	0.99	0.00	.	.	F	0.60	2.30
	Gln	329	A	A	1.39	-0.50	.	.	F	0.60	2.48
	Gln	330	A	A	1.63	-0.54	.	.	F	0.90	1.92
20	Thr	331	A	A	1.89	-0.11	.	*	F	0.60	2.20
	Asp	332	T	T	.	1.03	-0.90	.	.	F	1.70	2.54
	Ser	333	A	.	.	.	T	T	.	0.92	-0.66	.	.	F	1.70	1.09
	Gly	334	T	T	.	0.62	-0.37	.	.	F	1.25	0.62
	Lys	335	A	T	.	0.67	-0.47	*	*	F	0.85	0.50
25	Val	336	A	A	0.17	-0.47	*	*	F	0.45	0.74
	Leu	337	A	A	0.17	-0.17	*	*	F	0.45	0.62
	Ser	338	A	A	-0.12	-0.20	*	*	F	0.45	0.54
	Lys	339	A	A	0.33	0.30	*	*	F	-0.15	0.73
	Leu	340	A	A	-0.52	-0.34	*	*	.	0.45	1.74
30	Gln	341	A	A	0.33	-0.34	*	*	.	0.45	1.07
	Ala	342	A	A	1.14	-0.73	*	*	.	0.60	0.89
	Arg	343	A	A	0.63	-0.73	*	*	.	0.75	1.81
	Leu	344	A	A	0.30	-0.73	*	*	.	0.60	0.86
	Asp	345	A	A	1.11	-0.21	*	*	F	0.45	0.90
35	Asp	346	A	A	1.11	-0.71	*	*	F	0.75	0.79
	Leu	347	A	A	0.81	-0.71	*	*	F	0.90	1.60
	Trp	348	A	A	0.39	-0.71	*	*	F	0.75	0.67
	Glu	349	A	A	1.17	-0.23	*	.	F	0.45	0.58
	Asp	350	A	A	0.87	0.27	*	.	F	-0.15	0.96
40	Ile	351	A	A	0.06	-0.03	*	*	.	0.45	1.22
	Thr	352	A	A	0.83	-0.26	*	.	.	0.30	0.58
	His	353	A	A	1.12	0.24	*	.	.	-0.30	0.47
	Ser	354	A	A	1.12	0.24	*	.	.	0.13	1.13
	Leu	355	A	0.78	-0.04	*	*	.	1.21	1.36
45	His	356	A	1.63	-0.10	*	.	F	1.49	0.99
	Asp	357	T	T	.	1.64	-0.10	.	.	F	2.52	1.00
	Gln	358	T	T	.	1.64	-0.10	.	.	F	2.80	1.63
	Gly	359	T	T	.	1.13	-0.29	.	.	F	2.52	1.63
	His	360	T	T	.	1.60	-0.10	.	.	F	2.09	0.80
50	Ser	361	C	1.63	0.33	.	.	.	0.66	0.46
	His	362	C	1.42	-0.07	.	.	.	0.98	0.78
	Leu	363	C	1.03	-0.07	.	.	.	0.70	0.88
	Gly	364	C	0.99	-0.14	.	.	.	0.70	0.84
	Asp	365	C	0.63	-0.10	.	.	.	0.70	0.79
55	Pro	366	C	0.54	-0.17	.	.	.	0.85	1.22

Applicant's or agent's file reference number	PS112PCT	International appli	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> , line <u>N/A</u> .	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>21 September 1999</u>	Accession Number <u>PTA-736</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

<p>For receiving Office use only</p> <p><input checked="" type="checkbox"/> This sheet was received with the international application</p> <p>Authorized officer <u>Lyell Meadows</u> <u>PCT Operations - IAPD Team 1</u> <u>(703) 305-3745 (703) 305-3230 (FAX)</u></p>	<p>For International Bureau use only</p> <p><input type="checkbox"/> This sheet was received by the International Bureau on:</p> <p>Authorized officer</p>
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ATCC Deposit No. PTA-736**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-736**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PS112PCT	International application	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> , line <u>N/A</u> .	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u>	
Date of deposit <u>09 June 1999</u>	Accession Number <u>PTA-2071</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input type="checkbox"/> This sheet was received with the international application Authorized officer	For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer
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ATCC Deposit No. PTA-2071**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-2071**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

633

Applicant's or agent's file reference number	PS112PCT	International application	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 02 November 1999	Accession Number PTA-909
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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<input checked="" type="checkbox"/> This sheet was received with the international application
Authorized officer John Meadows PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FAX)

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Authorized officer

ATCC Deposit No. PTA-909**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-909**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

636

Applicant's or agent's file reference number	P-S112PCT	International applic	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>23</u> 47 , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 28 August 1997	Accession Number 209226
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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ATCC Deposit No. 209226**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209226**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

639

Applicant's or agent's file reference number	P3112PCT	International appli	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>2267</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 07 September 1999	Accession Number PTA-627
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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Authorized officer

ATCC Deposit No. PTA-627**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-627**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

642

Applicant's or agent's file reference number	PS112PCT	International applic:	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>236</u> <u>8</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 01 August 1997	Accession Number 209194
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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Authorized officer Lyell Meadows PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3220 (FAX)	<u>17 OCT 2000</u> Authorized officer

ATCC Deposit No. 209194**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209194**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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645

Applicant's or agent's file reference number	PS112PCT	International applic	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> <u>9</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 11 January 1999	Accession Number 203570
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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ATCC Deposit No. 203570**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203570**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

648

Applicant's or agent's file reference number	PS112PCT	International applic	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> <u>230</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 04 March 1998	Accession Number 209651
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input checked="" type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer L. J. Meadows PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FAX)	17 OCT 2000 Authorized officer

ATCC Deposit No. 209651**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 209651**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

651

Applicant's or agent's file reference number	PS112PCT	International appli	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> <u>230</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 09 May 2000	Accession Number PTA-1838
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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<input checked="" type="checkbox"/> This sheet was received with the international application
Authorized officer L. Meadows PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FAX)

For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received by the International Bureau on: 17 OCT 2000
Authorized officer

ATCC Deposit No. PTA-1838**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-1838**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

654

Applicant's or agent's file reference number	PS112PCT	International appl	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> <u>230</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 27 September 1999	Accession Number PTA-797
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input checked="" type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer: <u>Edell Meadows</u> PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FAX)	<u>17 OCT 2000</u> Authorized officer

ATCC Deposit No. PTA-797**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-797**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

657

Applicant's or agent's file reference number	PS112PCT	International app	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> <u>231</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 13 October 1999	Accession Number PTA-840
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only	For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received with the international application	<input checked="" type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer J. P. Meadows PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FAX)	<u>17 OCT 2000</u> Authorized officer

ATCC Deposit No. PTA-840**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-840**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

660

Applicant's or agent's file reference number	PS112PCT	International appl.	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> <u>231</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 07 June 1999	Accession Number PTA-181
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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<input checked="" type="checkbox"/> This sheet was received with the international application	<input checked="" type="checkbox"/> This sheet was received by the International Bureau on: <u>17 OCT 2000</u>
Authorized officer <u>Paul Meadows</u> PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FAX)	Authorized officer

ATCC Deposit No. PTA-181**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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ATCC Deposit No. PTA-181**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

Applicant's or agent's file reference number	PS112PCT	International application	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> <u>231</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 27 September 1999	Accession Number PTA-792
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only
<input checked="" type="checkbox"/> This sheet was received with the international application
Authorized officer: <u>Michael Meadows</u> PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 FAX

For International Bureau use only
<input checked="" type="checkbox"/> This sheet was received by the International Bureau on: <u>17 OCT 2000</u>
Authorized officer

ATCC Deposit No. PTA-792**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-792**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

666

Applicant's or agent's file reference number	S112PCT	International applica	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> <u>231</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 24 November 1999	Accession Number PTA-987
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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<input checked="" type="checkbox"/> This sheet was received with the international application	<input checked="" type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer: Meadows PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FAX)	17 OCT 2000 Authorized officer

ATCC Deposit No. PTA-987**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. PTA-987**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

669

Applicant's or agent's file reference number	S112PCT	International application number	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>228</u> <u>231</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 29 April 1999	Accession Number 203980
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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Authorized officer	Lysell Meadows PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FA)

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<input checked="" type="checkbox"/> This sheet was received by the International Bureau on: <u>17 OCT 2000</u>	
Authorized officer	

ATCC Deposit No. 203980**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203980**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

672

Applicant's or agent's file reference number	S112PCT	International application	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> <u>251</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 10 December 1998	Accession Number 203517
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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Authorized officer Michael Meadows PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FAX)	17 OCT 2000 Authorized officer

ATCC Deposit No. 203517**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203517**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

675

Applicant's or agent's file reference number	US112PCT	International application	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> <u>232</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 08 April 1999	Accession Number 203917
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application Authorized officer: James L. Meadows PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FAX)	For International Bureau use only <input checked="" type="checkbox"/> This sheet was received by the International Bureau on: <u>17 OCT 2000</u> Authorized officer:
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ATCC Deposit No. 203917**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

ATCC Deposit No. 203917**Page 3****DENMARK**

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

678

Applicant's or agent's file reference number	PS112PCT	International application	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> <u>232</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 16 October 1997	Accession Number 209368
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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Authorized officer: Meadows PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FAX)	17 OCT 2000 Authorized officer

ATCC Deposit No. 209368**Page 2****CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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ATCC Deposit No. 209368**Page 3****DENMARK**

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SWEDEN

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NETHERLANDS

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681

Applicant's or agent's file reference number	PS112PCT	International applic	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>226</u> <u>232</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 19 October 1998	Accession Number 203364
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

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ATCC Deposit No. 203364**Page 2****CANADA**

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NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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ATCC Deposit No. 203364**Page 3****DENMARK**

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SWEDEN

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NETHERLANDS

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684

Applicant's or agent's file reference number	PS112PCT	International application	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 25 September 1997	Accession Number 209300
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
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Authorized officer Lyell Meadows PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FAX)	17 OCT 2000 Authorized officer

ATCC Deposit No. 209300**Page 2****CANADA**

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UNITED KINGDOM

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ATCC Deposit No. 209300**Page 3****DENMARK**

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Applicant's or agent's file reference number	PS112PCT	International application	UNASSIGNED
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

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A. The indications made below relate to the microorganism referred to in the description on page <u>228</u> <u>231</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit 27 September 1999	Accession Number PTA-796
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
Europe In respect to those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28 (4) EPC).	
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For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application Authorized officer: <u>Eric Meadows</u> PCT Operations - IAPD Team 1 (703) 305-3745 (703) 305-3230 (FAX)	For International Bureau use only <input checked="" type="checkbox"/> This sheet was received by the International Bureau on: <u>17 OCT 2000</u> Authorized officer:
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ATCC Deposit No. PTA-796**Page 2****CANADA**

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ATCC Deposit No. PTA-796**Page 3****DENMARK**

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What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group
5 consisting of:

(a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

10 (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

15 (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;

(e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X,
20 having biological activity;

(f) a polynucleotide which is a variant of SEQ ID NO:X;

(g) a polynucleotide which is an allelic variant of SEQ ID NO:X;

(h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;

25 (i) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.
- 5 3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.
- 10 4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.
- 15 5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
- 20 6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.
- 25 7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.
8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.
- 30 9. A recombinant host cell produced by the method of claim 8.
10. The recombinant host cell of claim 9 comprising vector sequences.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

5 (b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;

(c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

10 (d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

15 (g) a variant of SEQ ID NO:Y;

(h) an allelic variant of SEQ ID NO:Y; or

(i) a species homologue of the SEQ ID NO:Y.

20 12. The isolated polypeptide of claim 11, wherein the secreted form or the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

25 14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:

30 (a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount
5 of the polypeptide of claim 11 or the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of
10 claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to
15 a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.
20

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the
25 polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

22. A method of identifying an activity in a biological assay, wherein the
30 method comprises:

(a) expressing SEQ ID NO:X in a cell;

(b) isolating the supernatant;

- (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 20.

1/22

1 GGGCCATCAGGCCCCACAGAGGAGGGCGGCCTCCACGTCCACATGGAGTTCCCGGGGGCGG 60
1 A I R P T E E G G L H V H M E F P G A D 20

61 ACGGCTGTAACCAGGTGGATGCCGAGTACCTGAAGGTGGGCTCCGAGGGACACTTCAGAG 120
21 G C N Q V D A E Y L K V G S E G H F R V 40

121 TCCCGGCCTTGGGCTACCTGGACGTGCGCATCGTGGACACAGACTACAGCTCCTTCGCCC 180
41 P A L G Y L D V R I V D T D Y S S F A V 60

181 TCCTTTACATCTACAAGGAGCTGGAGGGGGCGCTCAGCACCATGGTGCAGCTCTACAGCC 240
61 L Y I Y K E L E G A L S T M V Q L Y S R 80

241 GGACCCAGGATGTGAGTCCCCAGGCTCTGAAGGCCTTCCAGGACTTCTACCCGACCCTGG 300
81 T Q D V S P Q A L K A F Q D F Y P T L G 100

301 GGCTCCCCGAGGACATGATGGTCATGCTGCCCCAGTCAGATGCATGCAACCCTGAGAGCA 360
101 L P E D M M V M L P Q S D A C N P E S K 120

361 AGGAGGCGCCCTGACACCTCCGGAGCCCCACCCCGCCCTTCCAGGTGGAGCCAAAGCA 420
121 E A P * 124

421 GCAGGCGCCTTTGCCCTGGAGTCAAGACCCACAGCCCTCGGGACCACCTGGAGTCTCT 480

481 CCATCCTCACCCCCCGCCTGTGGGATGCCTTGTGGGACGTCTCTTTCTATTCAATAAAC 540

541 AGATGCTGCAGCCTCAAAAAAAAAAAAAAA 570

FIG. 1

2/22

	10	20	30	40	
1	-----				Lipocolon.aa
1	MKGLVLSFAL	-VALSALCVYGDVPIQP	DFQEDKILGK	WYG	emb CAA48138.1
1	MMRILLALS	LGVACCSLWVGAEVQVQP	DFQKEKVLGK	WYG	dbj BAA12075.1
1	MMRILLALS	LGVACCSLWVGAEVQVQP	DFQKEKVLGK	WYG	emb CAA59132.1
	50	60	70	80	
1	-----	AIRPTEEGGLHVHMEFP	G		Lipocolon.aa
40	IGLASNSNW	FQSKKQQLKMCTTVI	ITPTADGNLDV	VATFPK	emb CAA48138.1
41	IGLASNSNW	FQSKKQQLKMCTTVI	ITPTADGNVEV	TATYPK	dbj BAA12075.1
41	IGLASNSNW	FQSKKQQLKMCTTVI	ITPTADGNLEV	TATYPK	emb CAA59132.1
	90	100	110	120	
19	ADGCNOVDAEY	LKVGSEGHFRVPALGY	---	LDVRIVDTDY	Lipocolon.aa
80	LDRCCEKKSMTY	IKTEQPGRF	LSKSPRYGSDH	VRVVESNY	emb CAA48138.1
81	MDRCETKSMTY	FKTEQLGRF	RAKSPRYGSEH	DMRVVETNY	dbj BAA12075.1
81	MDRCETKSMTY	FKTEQLGRF	RAKSPRYGSEH	DMRVVETNY	emb CAA59132.1
	130	140	150	160	
56	SSFAVLIIYKE	LEGALSTMVOLYSRTQDV	SPOALKAFQDF		Lipocolon.aa
120	DEYTLMH	TIKTKGNEVNTIVS	LFGRRKTLSP	ELLDKFQQF	emb CAA48138.1
121	DEYILM	YTVKTKGSETNQIVS	LFGRDKDLR	PELLDKFQNF	dbj BAA12075.1
121	DEYILM	YTVKTKGSETNQIVS	LFGRDKDLR	PELLDKFQNF	emb CAA59132.1
	170	180			
96	YPTLGLPEDMMV	MLPQSDACNPESKEAP			Lipocolon.aa
160	AKEQGLTDDN	ILILPQTDSCMSEV			emb CAA48138.1
161	AKSQGLADDN	IIILPHTDQCMTEA			dbj BAA12075.1
161	AKSQGLADDN	IIILPHTDQCMTEA			emb CAA59132.1

FIG. 2

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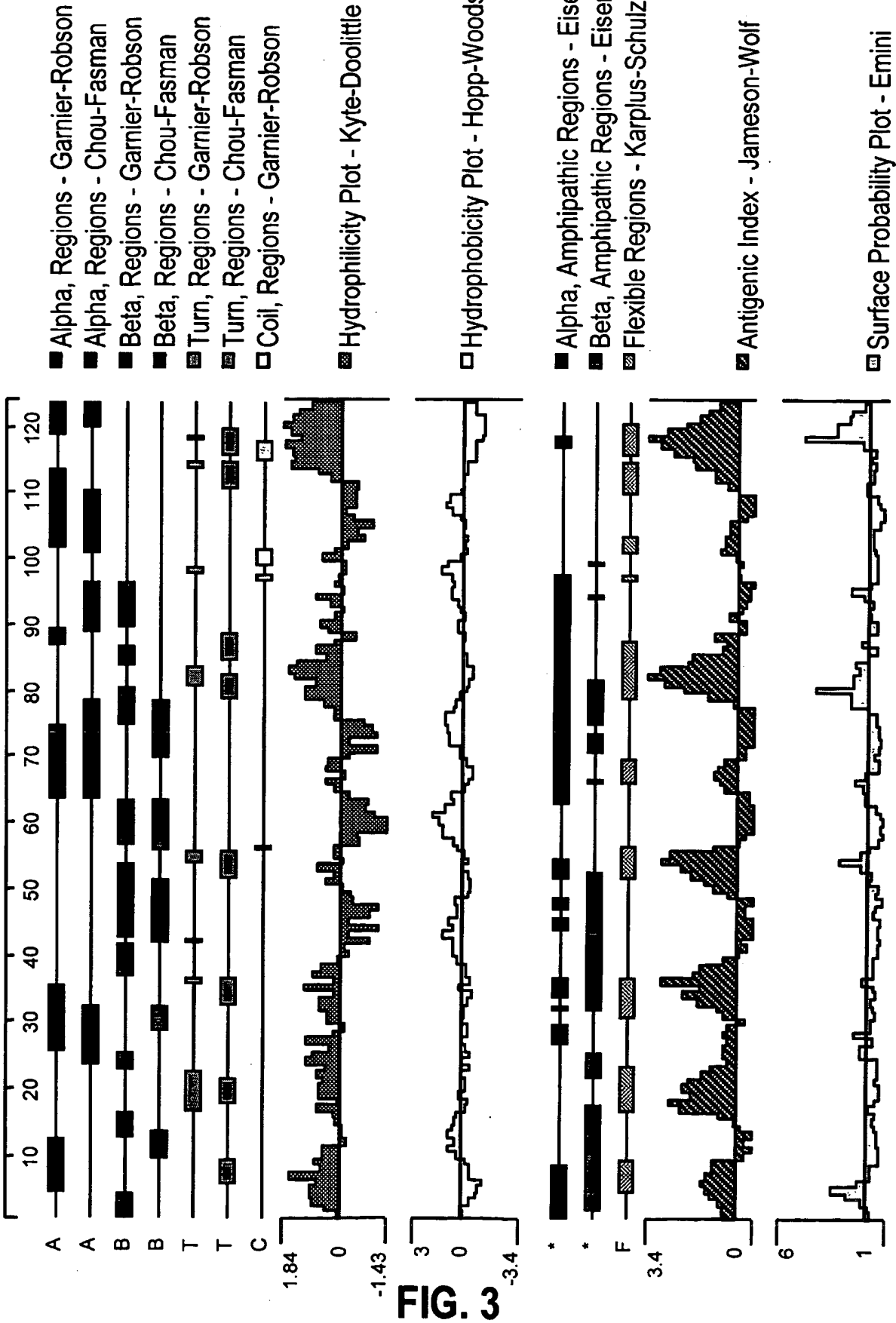


FIG. 3

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1 TCGACGGCAGAGGAGCACTTAGCAGCTTATTCAGTGTCCGATTCTGATTCCGGCAAGGAT 60
61 CCAAGCATGGAATGCTGCCGTCGGGCAACTCCTGGCACACTGCTCCTCTTTCTGGCTTTC 120
1 M E C C R R A T P G T L L L F L A F 18
121 CTGCTCCTGAGTTCCAGGACCGCACGCTCCGAGGAGGACCGGGACGGCCTATGGGATGCC 180
19 L L L S S R T A R S E E D R D G L W D A 38
181 TGGGGCCCATGGAGTGAATGCTCACGCACCTGCGGGGTGGGGCCTCCTACTCTCTGAGG 240
39 W G P W S E C S R T C G G G A S Y S L R 58
241 CGCTGCCTGAGCAGCAAGAGCTGTGAAGGAAGAAATATCCGATACAGAACATGCAGTAAT 300
59 R C L S S K S C E G R N I R Y R T C S N 78
301 GTGGACTGCCCACCAGAAGCAGGTGATTTCCGAGCTCAGCAATGCTCAGCTCATAATGAT 360
79 V D C P P E A G D F R A Q Q C S A H N D 98
361 GTCAAGCACCATGGCCAGTTTTATGAATGGCTTCCTGTGTCTAATGACCCTGACAACCCA 420
99 V K H H G Q F Y E W L P V S N D P D N P 118
421 TGTTCACCTCAAGTGCCAAGCCAAAGGAACAACCCTGGTTGTTGAACTAGCACCTAAGGTC 480
119 C S L K C Q A K G T T L V V E L A P K V 138
481 TTAGATGGTACGCGTTGCTATACAGAATCTTTGGATATGTGCATCAGTGGTTTATGCCAA 540
139 L D G T R C Y T E S L D M C I S G L C Q 158
541 ATTGTTGGCTGCGATCACCAGCTGGGAAGCACCGTCAAGGAAGATAACTGTGGGGTCTGC 600
159 I V G C D H Q L G S T V K E D N C G V C 178
601 AACGGAGATGGGTCCACCTGCCGGCTGGTCCGAGGGCAGTATAAATCCCAGCTCTCCGCA 660
179 N G D G S T C R L V R G Q Y K S Q L S A 198
661 ACCAAATCGGATGATACTGTGGTTGCAATCCCTATGGAAGTAGACATATTCGCCTTGTC 720
199 T K S D D T V V A I P Y G S R H I R L V 218

FIG. 4A

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721 TTAAAAGGTCCTGATCACTTATATCTGGAAACCAACCTCCAGGGGACTAAAGGTGAA 780
219 L K G P D H L Y L E T K T L Q G T K G E 238

781 AACAGTCTCAGCTCCACAGGAACCTTTCCTTGTGGACAATTCTAGTGTGGACTTCCAGAAA 840
239 N S L S S T G T F L V D N S S V D F Q K 258

841 TTTCCAGACAAAGAGATACTGAGAATGGCTGGACCACTCACAGCAGATTTTCATTGTCAAG 900
259 F P D K E I L R M A G P L T A D F I V K 278

901 ATTCTGTAACCTCGGGCTCCGCTGACAGTACAGTCCAGTTCATCTTCTATCAACCCATCATC 960
279 I R N S G S A D S T V Q F I F Y Q P I I 298

961 CACCGATGGAGGGAGACGGATTTCTTTTCCTTGCTCAGCAACCTGTGGAGGAGGTTATCAG 1020
299 H R W R E T D F F P C S A T C G G G Y Q 318

1021 CTGACATCGGCTGAGTGCTACGATCTGAGGAGCAACCGTGTGGTTGCTGACCAATACTGT 1080
319 L T S A E C Y D L R S N R V V A D Q Y C 338

1081 CACTATTACCCAGAGAACATCAAACCCAAACCCAGCTTCAGGAGTGCAACTTGGATCCT 1140
339 H Y Y P E N I K P K P K L Q E C N L D P 358

1141 TGTCCAGCCAGGTGGGAGGCCACCCCATGGACCGCTGCTCCTCCTCGTGTGGGGGGGGC 1200
359 C P A R W E A T P W T A C S S S C G G G 378

1201 ATCCAGAGCCGGGCAGTTTCCTGTGTGGAGGAGACATCCAGGGGCATGTCACTTCAGTG 1260
379 I Q S R A V S C V E E D I Q G H V T S V 398

1261 GAAGAGTGGAATGCATGTACACCCCTAAGATGCCCATCGCGCAGCCCTGCAACATTTTT 1320
399 E E W K C M Y T P K M P I A Q P C N I F 418

1321 GACTGCCCTAAATGGCTGGCACAGGAGTGGTCTCCGTGCACAGTGACATGTGGCCAGGGC 1380
419 D C P K W L A Q E W S P C T V T C G Q G 438

1381 CTCAGATACCGTGTGGTCCTCTGCATCGACCATCGAGGAATGCACACAGGAGGCTGTAGC 1440
439 L R Y R V V L C I D H R G M H T G G C S 458

FIG. 4B

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1441 CCAAAAACAAAGCCCCACATAAAAGAGGAATGCATCGTACCCACTCCCTGCTATAAACCC 1500
459 P K T K P H I K E E C I V P T P C Y K P 478

1501 AAAGAGAACTTCCAGTCGAGGCCAAGTTGCCATGGTTCAAACAAGCTCAAGAGCTAGAA 1560
479 K E K L P V E A K L P W F K Q A Q E L E 498

1561 GAAGGAGCTGCTGTGTCAGAGGAGCCCTCGTTCATCCCAAAGGCCTGGTCGGCCTGCACA 1620
499 E G A A V S E E P S F I P K A W S A C T 518

1621 GTCACCTGTGGTGTGGGGACCCAGGTGCGAATAGTCAGGTGCCAGGTGCTCCTGTCTTTC 1680
519 V T C G V G T Q V R I V R C Q V L L S F 538

1681 TCTCAGTCCGTGGCTGACCTGCCTATTGACGAGTGTGAAGGGCCCAAGCCAGCATCCAG 1740
539 S Q S V A D L P I D E C E G P K P A S Q 558

1741 CGTGCCTGTTATGCAGGCCCATGCAGCGGGAAATTCCTGAGTTCAACCCAGACGAGACA 1800
559 R A C Y A G P C S G E I P E F N P D E T 578

1801 GATGGGCTCTTTGGTGGCCTGCAGGATTTGACGAGCTGTATGACTGGGAGTATGAGGGG 1860
579 D G L F G G L Q D F D E L Y D W E Y E G 598

1861 TTCACCAAGTGCTCCGAGTCCTGTGGAGGAGGTGTCCAGGAGGCTGTGGTGAGCTGCTTG 1920
599 F T K C S E S C G G G V Q E A V V S C L 618

1921 AACAAACAGACTCGGGAGCCTGCTGAGGAGAACCTGTGCGTGACCAGCCGCCGCCCCCA 1980
619 N K Q T R E P A E E N L C V T S R R P P 638

1981 CAGCTCCTGAAGTCCTGCAATTTGGATCCCTGCCAGCAAGGTGGGAAATTGGCAAGTGG 2040
639 Q L L K S C N L D P C P A R W E I G K W 658

2041 AGTCCATGTAGTCTCACATGTGGGGTCGGCCTACAGACCAGAGACGTCTTCTGCAGCCAC 2100
659 S P C S L T C G V G L Q T R D V F C S H 678

2101 CTGCTTTCCAGAGAGATGAATGAAACAGTCATCCTGGCTGATGAGCTGTGTCGCCAGCCC 2160
679 L L S R E M N E T V I L A D E L C R Q P 698

FIG. 4C

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2161 AAGCCCAGCACGGTGCAAGCTTGTAACCGCTTTAATTGCCCCCAGCCTGGTACCCTGCA 2220
699 K P S T V Q A C N R F N C P P A W Y P A 718

2221 CAGTGGCAGCCGTGTTCCAGAACGTGTGGCGGGGGTGTTCAGAAACGTGAGGTTCTTTGC 2280
719 Q W Q P C S R T C G G G V Q K R E V L C 738

2281 AAGCAGCGCATGGCTGATGGCAGCTTCCTGGAGCTTCCTGAGACCTTCTGTTTCAGCTTCA 2340
739 K Q R M A D G S F L E L P E T F C S A S 758

2341 AAACCTGCCTGCCAGCAAGCATGCAAGAAAGATGACTGTCCCAGCGAGTGGCTTCTCTCA 2400
759 K P A C Q Q A C K K D D C P S E W L L S 778

2401 GACTGGACAGAGTGTTCACAAGCTGCGGGGAAGGCACCCAGACTCGAAGCGCCATTTCG 2460
779 D W T E C S T S C G E G T Q T R S A I C 798

2461 CGAAAGATGCTGAAAACCGGCCTCTCAACGTTGTCAATTCCACCCTGTGCCCGCCCCTG 2520
799 R K M L K T G L S T V V N S T L C P P L 818

2521 CCTTTCTCTTCTCCATCAGGCCCTGTATGCTGGCAACCTGTGCAAGGCCCGGGCGGCCA 2580
819 P F S S S I R P C M L A T C A R P G R P 838

2581 TCCACGAAGCACAGCCCGCACATCGCGGCCGCCAGGAAGGTCTACATACAGACTCGCAGG 2640
839 S T K H S P H I A A A R K V Y I Q T R R 858

2641 CAGAGGAAGCTGCACTTCGTGGTGGGGGGCTTCGCCTACCTGCTCCCCAAGACGGCGGTG 2700
859 Q R K L H F V V G G F A Y L L P K T A V 878

2701 GTGCTGCGCTGCCCCGGCGCGCAGGGTCCGCAAGCCCCTCATCACCTGGGAGAAGGACGGC 2760
879 V L R C P A R R V R K P L I T W E K D G 898

2761 CAGCACCTCATCAGCTCGACGCACGTACGGTGGCCCCCTTCGGCTATCTCAAGATCCAC 2820
899 Q H L I S S T H V T V A P F G Y L K I H 918

2821 CGCCTCAAGCCCTCGGATGCAGGCGTCTACACCTGCTCAGCGGGCCCCGGCCGGGAGCAC 2880
919 R L K P S D A G V Y T C S A G P A R E H 938

FIG. 4D

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2881	TTTGTGATTAAGCTCATCGGAGGCAACCGCAAGCTCGTGGCCCGGCCCTTGAGCCCGAGA	2940
939	F V I K L I G G N R K L V A R P L S P R	958
2941	AGTGAGGAAGAGGTGCTTGCGGGGAGGAAGGGCGGCCCGAAGGAGGCCCTGCAGACCCAC	3000
959	S E E E V L A G R K G G P K E A L Q T H	978
3001	AAACACCAGAACGGGATCTTCTCCAACGGCAGCAAGGCGGAGAAGCGGGGCCTGGCCGCC	3060
979	K H Q N G I F S N G S K A E K R G L A A	998
3061	AACCCGGGGAGCCGCTACGACGACCTCGTCTCCCGGCTGCTGGAGCAGGGCGGCTGGCCC	3120
999	N P G S R Y D D L V S R L L E Q G G W P	1018
3121	GGAGAGCTGCTGGCCTCGTGGGAGGCGCAGGACTCTGCGAAAGGAACACGACCTCGGAG	3180
1019	G E L L A S W E A Q D S A E R N T T S E	1038
3181	GAGGACCCGGGTGCAGAGCAAGTGCTCCTGCACCTGCCCTTCACCATGGTGACCGAGCAG	3240
1039	E D P G A E Q V L L H L P F T M V T E Q	1058
3241	CGGCGCCTGGACGACATCCTGGGGAACCTCTCCAGCAGCCCGAGGAGCTGCGCGACCTC	3300
1059	R R L D D I L G N L S Q Q P E E L R D L	1078
3301	TACAGCAAGCACCTGGTGGCCCAGCTGGCCCAGGAGATCTTCCGCAGCCACCTGGAGCAC	3360
1079	Y S K H L V A Q L A Q E I F R S H L E H	1098
3361	CAGGACACGCTCCTGAAGCCCTCGGAGCGCAGGACTTCCCCAGTGACTCTCTCGCCTCAT	3420
1099	Q D T L L K P S E R R T S P V T L S P H	1118
3421	AAACACGTGTCTGGCTTCAGCAGCTCCCTGCGGACCTCCTCCACCGGGGACGCCGGGGGA	3480
1119	K H V S G F S S S L R T S S T G D A G G	1138
3481	GGCTCTCGAAGGCCACACCGCAAGCCCACCATCCTGCGCAAGATCTCAGCGGCCAGCAG	3540
1139	G S R R P H R K P T I L R K I S A A Q Q	1158
3541	CTCTCAGCCTCGGAGGTGGTCACCCACCTGGGGCAGACGGTGGCCCTGGCCAGCGGGACA	3600
1159	L S A S E V V T H L G Q T V A L A S G T	1178

FIG. 4E

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3601	CTGAGTGTCTTCTGCACTGTGAGGCCATCGGCCACCAAGGCCTACCATCAGCTGGGCC	3660
1179	L <u>S V L L H C E A I G H P R P T I S W A</u>	1198
3661	AGGAATGGAGAAGAAGTTCAGTTCAGTGACAGGATTCTTCTACAGCCAGATGATTCCTTA	3720
1199	<u>R N G E E V Q F S D R I L L Q P D D S L</u>	1218
3721	CAGATCTTGGCACCAGTGGAAGCAGATGTGGGTTTCTACACTTGCAATGCCACCAATGCC	3780
1219	<u>Q I L A P V E A D V G F Y T C N A T N A</u>	1238
3781	TTGGGATACGACTCTGTCTCCATTGCCGTCACATTAGCAGGAAAGCCACTAGTGAAAACG	3840
1239	<u>L G Y D S V S I A V T L A G K P L V K T</u>	1258
3841	TCACGAATGACAGTGATCAACACGGAGAAGCCTGCAGTCACAGTCGATATAGGAAGCACC	3900
1259	<u>S R M T V I N T E K P A V T V D I G S T</u>	1278
3901	ATCAAAACAGTGCAGGGAGTGAATGTGACAATCAACTGCCAGGTTGCAGGAGTGCCTGAA	3960
1279	<u>I K T V Q G V N V T I N C Q V A G V P E</u>	1298
3961	GCTGAAGTCACTTGGTTCAGGAATAAAAGCAAACCTGGGCTCCCCGCACCATCTGCACGAA	4020
1299	<u>A E V T W F R N K S K L G S P H H L H E</u>	1318
4021	GGCTCCTTGCTGCTCACAAACGTGTCCTCCTCGGATCAGGGCCTGTACTCCTGCAGGGCG	4080
1319	<u>G S L L L T N V S S S D Q G L Y S C R A</u>	1338
4081	GCCAATCTTCATGGAGAGCTGACTGAGAGCACCAGCTGCTGATCCTAGATCCCCCCAA	4140
1339	<u>A N L H G E L T E S T Q L L I L D P P Q</u>	1358
4141	GTCCCCACACAGTTGGAAGACATCAGGGCCTTGCTCGCTGCCACTGGACCGAACCTTCCT	4200
1359	<u>V P T Q L E D I R A L L A A T G P N L P</u>	1378
4201	TCAGTGCTGACGTCTCCTCTGGGAACACAGCTGGTCTGGATCCTGGGAATTCTGCTCTC	4260
1379	<u>S V L T S P L G T Q L V L D P G N S A L</u>	1398
4261	CTTGGCTGCCCCATCAAAGGTCACCCTGTCCCTAATATCACCTGGTTTCATGGTGGTCAG	4320
1399	<u>L G C P I K G H P V P N I T W F H G G Q</u>	1418

FIG. 4F

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4321	CCAATTGTCACTGCCACAGGACTGACGCATCACATCTTGGCAGCTGGACAGATCCTTCAA	4380
1419	<u>P I V T A T G L T H H I L A A G Q I L Q</u>	1438
4381	GTTGCAAACCTTAGCGGTGGGTCTCAAGGGAATTCAGCTGCCTTGCTCAGAATGAGGCA	4440
1439	<u>V A N L S G G S Q G E F S C L A Q N E A</u>	1458
4441	GGGGTGCTCATGCAGAAGGCATCTTTAGTGATCCAAGATTACTGGTGGTCTGTGGACAGA	4500
1459	<u>G V L M Q K A S L V I Q D</u> Y <u>W W S V D R</u>	1478
4501	CTGGCAACCTGCTCAGCCTCCTGTGGTAACCGGGGGTTCAGCAGCCCCGCTTGAGGTGC	4560
1479	<u>L A T C S A S C G N R G V Q Q P R L R C</u>	1498
4561	CTGCTGAACAGCACGGAGGTCAACCCTGCCCCACTGCGCAGGGAAGGTTTCGCCCTGCGGTG	4620
1499	<u>L L N S T E V N P A H C A G K V R P A V</u>	1518
4621	CAGCCCATCGCGTGCAACCGGAGAGACTGCCCTTCTCGGTGGATGGTGACCTCCTGGTCT	4680
1519	<u>Q P I A C N R R D C P S R</u> <u>W M V T S W S</u>	1538
4681	GCCTGTACCCGGAGCTGTGGGGGAGGTGTCCAGACCCGCAGGGTGACCTGTCAAAGCTG	4740
1539	<u>A C T R S C G G G V Q T R R V T C Q K L</u>	1558
4741	AAAGCCTCTGGGATCTCCACCCCTGTGTCCAATGACATGTGCACCCAGGTGCGCAAGCGG	4800
1559	<u>K A S G I S T P V S N D M C T Q V A K R</u>	1578
4801	CCTGTGGACACCCAGGCCTGTAACCAGCAGCTGTGTGTGGAGTGGGCCTTCTCCAGCTGG	4860
1579	<u>P V D T Q A C N Q Q L C V E</u> <u>W A F S S W</u>	1598
4861	GGCCAGTGCAATGGGCCTTGCATCGGGCCTCACCTAGCTGTGCAACACAGACAAGTCTTC	4920
1599	<u>G Q C N G P C I G P H L A V Q H R Q V F</u>	1618
4921	TGCCAGACACGGGATGGCATCACCTTACCATCAGAGCAGTGAGTGCTCTTCCGAGGCCT	4980
1619	<u>C Q T R D G I T L P S E Q C S A L P R P</u>	1638
4981	GTGAGCACCCAGAACTGCTGGTCAGAGGCCTGCAGTGTACACTGGAGAGTCAGCCTGTGG	5040
1639	<u>V S T Q N C W S E A C S V H</u> <u>W R V S L W</u>	1658

FIG. 4G

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5041 ACCCTGTGCACAGCTACCTGTGGCAACTACGGCTTCCAGTCCCGGCGTGTGGAGTGTGTG 5100
1659 T L C T A T C G N Y G F Q S R R V E C V 1678

5101 CATGCCCCGACCAACAAGGCAGTGCCTGAGCACCTGTGCTCCTGGGGGCCCCGGCCTGCC 5160
1679 H A R T N K A V P E H L C S W G P R P A 1698

5161 AACTGGCAGCGCTGCAACATCACCCTGTGAAAACATGGAGTGCAGAGACACCACCAGG 5220
1699 N W Q R C N I T P C E N M E C R D T T R 1718

5221 TACTGCGAGAAGGTGAAACAGCTGAACTCTGCCAACTCAGCCAGTTTAAATCTCGCTGC 5280
1719 Y C E K V K Q L K L C Q L S Q F K S R C 1738

5281 TGTGGAACCTGTGGCAAAGCGTGAAGATAGGGTGTGGGGA AAAACTCTACCCTGGCCACA 5340
1739 C G T C G K A * 1746

5341 CGAAGGACTCAGCAACCACCTCGGACAGAACCTAAGCTTTCTTCATTTTATTTATTTAT 5400

5401 TTCCCCCTCCCCACTCCACACACACCCTTCCAACCTCCTCCACCTCCACCTTCAAGCATA 5460

5461 AGGACGTCCGCGTGT TTTCTCTTT CAGTTAGCTGGAGGACAGGATGTTGGGAAAGGAAAG 5520

5521 GACAGATGTCTAAAGGAGGTTGCAGAGCAGGCCAGGCAGACAGTGGGGGCTCCCTTGAAG 5580

5581 AGCTTCCTCCCTCCCAAACCTGGGTCTCAAAGACCTAGAAAGAGGCAGGCACAGCCCCTG 5640

5641 CGGACAGCAGGGAGCCAGAAGGTTTGTAGCCTATTGGTGCAAACATTGGACAAATTCCTG 5700

5701 TGTCTTTCCTAGAAGCGCAG 5720

FIG. 4H

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FIG. 5A

	10	20	30	40	
1	M E C C R R A T P G T L L L F L A F L L L S S R T A R S E E D R D G L - W D A W	THRAP			
1	M K C - - - S Y T V V F L L F - - Y L L I A S F H V - - - - - D A L S W A A W	emb CAB03121.1			
	50	60	70	80	
40	G P W S E C S R T C G G G A S Y S L R R C L S S K S C E G R N I R Y R T C S N V	THRAP			
30	S P W S S C T K T C G G G V S R Q L R R C L T S K - C S G E S V R F K V C A Q K	emb CAB03121.1			
	90	100	110	120	
80	D C P P E A G D F R A Q Q C S A H N D V K H H G Q F Y E W L P V S N D P D N P C	THRAP			
69	T C E S K S R L A R D T I C G G E - E I V S R G Q - - - - - - - - - - - C	emb CAB03121.1			
	130	140	150	160	
120	S L K C Q A K G T T L V V E L A P K V L D G T R C - Y T E S L D M C I S G L C Q	THRAP			
94	E V V C R S R L T G - - A N F L W R V D D G T P C Q A A T S R A V C S K G S C Q	emb CAB03121.1			
	170	180	190	200	
159	I V G C D H Q L G S T V K E D N C G V C N G D G S T C R L V R G Q Y K S Q L S A	THRAP			
132	I V G C D G L I S S S F R F D A C G V C G G R G D T C D - - - - - - - - - -	emb CAB03121.1			
	210	220	230	240	
199	T K S D D T V V A I P Y G S R H I R L V L K G P D H L Y L E T K T L Q G T K G E	THRAP			
160	- - - - - - - - - - N G K F I W K V S E E - Y - - - - - T A C A S N C D	emb CAB03121.1			
	250	260	270	280	
239	N S L S S T G T F L V D N S S V D F Q K F P D K E I L R M A G P L T A D F I V K	THRAP			
180	D I V D W S G A - - - - - - - - - - - G R S I A S T S Q P I V V - - - - -	emb CAB03121.1			
	290	300	310	320	
279	I R N S G S A D S T V Q F I F Y O P I I H R W R E T D F F P C S A T C G G G Y Q	THRAP			
201	- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -	emb CAB03121.1			
	330	340	350	360	
319	L T S A E C Y D L R S N R V V A D O Y C H Y Y P E N I K P K P K L O E C N L D P	THRAP			
201	- - - - - C V N A I T G R V V P E K L C - - - A D K L R P K V E A R P C P M L I	emb CAB03121.1			

FIG. 5B

370 380 390 400

359 C P A R W E A T P W T A C S S S C G G G I O S R A V S C V E E D I Q G H V T S V THRAP
233 C P S R W M A A D W T E C V P H C G E G T R K R E V Y C V Q T A H N V T V H V P emb CAB03121.1

410 420 430 440

399 E E W K C M Y T P K M P I A Q P C N I F D C P K W L A Q E W S P C T V T C G Q G THRAP
273 D T F - C E N G T R P A A E E N C V S T S C G R W E A G K W S K C T A S C G Q G emb CAB03121.1

450 460 470 480

439 L R Y R V V L C I D H R G M H T G G C S P K T K P H I K E E C I V P T P C Y K P THRAP
312 V R R R H V A C V G - - - - G S D C D E G G R P R Q E T T C Y A G I P C S I A emb CAB03121.1

490 500 510 520

479 K E K L P V E A K L P W F K Q A Q E L E - - E G A A V S E E P S F I P K A W S A THRAP
347 T N S L D W N D R A - - Y L D G N T F G S M D N H N D W Q A P R L V A G E W S T emb CAB03121.1

530 540 550 560

517 C T V T C G V G T Q V R I V R C Q V L L S F S Q S V A D L P I D E C E G P K P A THRAP
385 C S S T C G T G V M S R T V E C V A V N P I S S A P I K L P M S E C Q D Q E Q P emb CAB03121.1

570 580 590 600

557 S Q - R A C Y A G P C S - G E I P E F N P D E T D G L F G G L Q D F D E L Y D W THRAP
425 K L F E S C E V R S C P L Q E D S K L S E D E A P - - - - - Y Q W emb CAB03121.1

610 620 630 640

595 E Y E G F T K C S E S C G G G V Q E A V V S C L N K Q T R E P A E E N L C V T S THRAP
453 R Y G D W T Q C S A S C L G G K Q K A A L K C I Q V S T G K S V Q W S Q C D A R emb CAB03121.1

650 660 670 680

635 R R P P O L L K S C N L D P C P A R W E I G K W S P C S L T C G V G L O T R D V THRAP
493 R R P P E K S R P C N Q H P C P P F W L T S K Y S D C S M S C G S G T A R R S V emb CAB03121.1

690 700 710 720

675 F C S H L L S R E - - M N E T V I L A D E L C R O P K P S T V Q A C N R F N C P THRAP
533 K C A O T V S K T D G A D A H I V L R D D R C H F K K P O E T E T C N V V A C P emb CAB03121.1

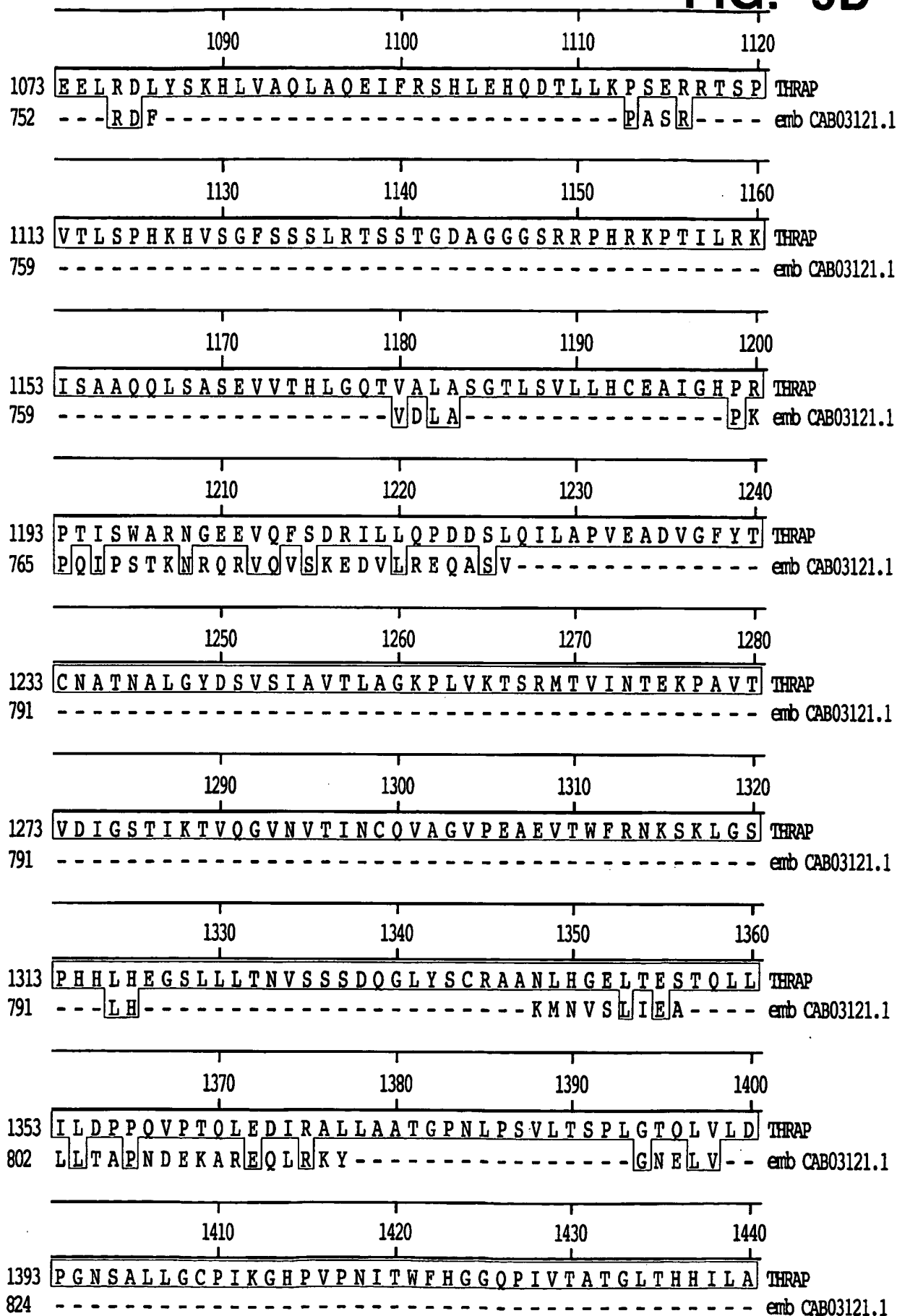
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FIG. 5C

	730	740	750	760	
713	PAWYPAQWQPCSRTCGGGVQKREVLCKORMADGSFLELPE				THRAP
573	ATW-----VSSLNKRHNKIKNLNLKTA-----				emb CAB03121.1
	770	780	790	800	
753	TFCSASKPACQQACKKDDCPSEWLLSDWTECSTSCGEGTQ				THRAP
595	-----QWTECSRISCDSEGER				emb CAB03121.1
	810	820	830	840	
793	TRSAICRKMLKTGLSTVVNSTLCPPLPFSSSIRPCMLATC				THRAP
609	RRQVWCIEIRDSRGKTQRRPDVECDANTKPTVEVCISFGSC				emb CAB03121.1
	850	860	870	880	
833	ARPGRPSTKHSPHIAAARKVYIQTRRQRKLHFVVGGFAYL				THRAP
649	SRPE-----LLSNRVFEQNAEQKKLTLGIGVATL				emb CAB03121.1
	890	900	910	920	
873	LPKTAVVLRCPARRVRKPLITWEKDGOHLISSTHVTVAPF				THRAP
679	YQGTSIKIKCPAKKFDKKKIYWKKNGKKIKNDAAIKV SAN				emb CAB03121.1
	930	940	950	960	
913	GYLKIHLRLKPSDAGVYTCSAGPAREHFVIKLI GG NRKLVA				THRAP
719	GNL RVFHARMEDAGVYEC-----FTDRLQG-----				emb CAB03121.1
	970	980	990	1000	
953	RPLSPRSEEEVLGRKG GPKEALQTHKHONGIFSNGSKAE				THRAP
744	-----				emb CAB03121.1
	1010	1020	1030	1040	
993	KRGLAANPGSRYDDLVSRLLEQGGWP GELLASWEAODSAE				THRAP
744	-----				emb CAB03121.1
	1050	1060	1070	1080	
1033	RNTTSEEDPGAEOVLLHLPFTMVTEQRRLDDILGNLSQOP				THRAP
744	-----NVTLNFKY-----				emb CAB03121.1

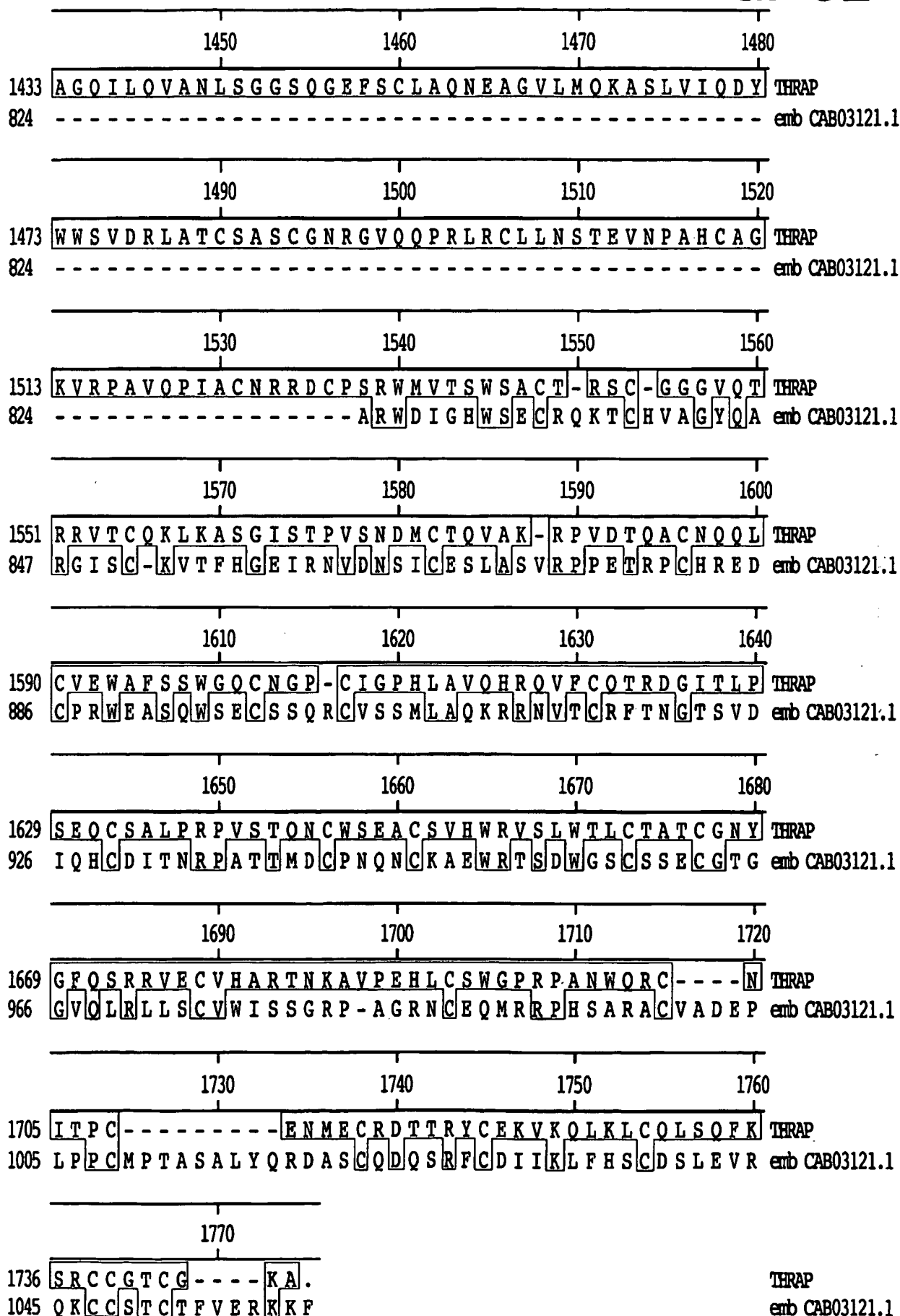
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FIG. 5D

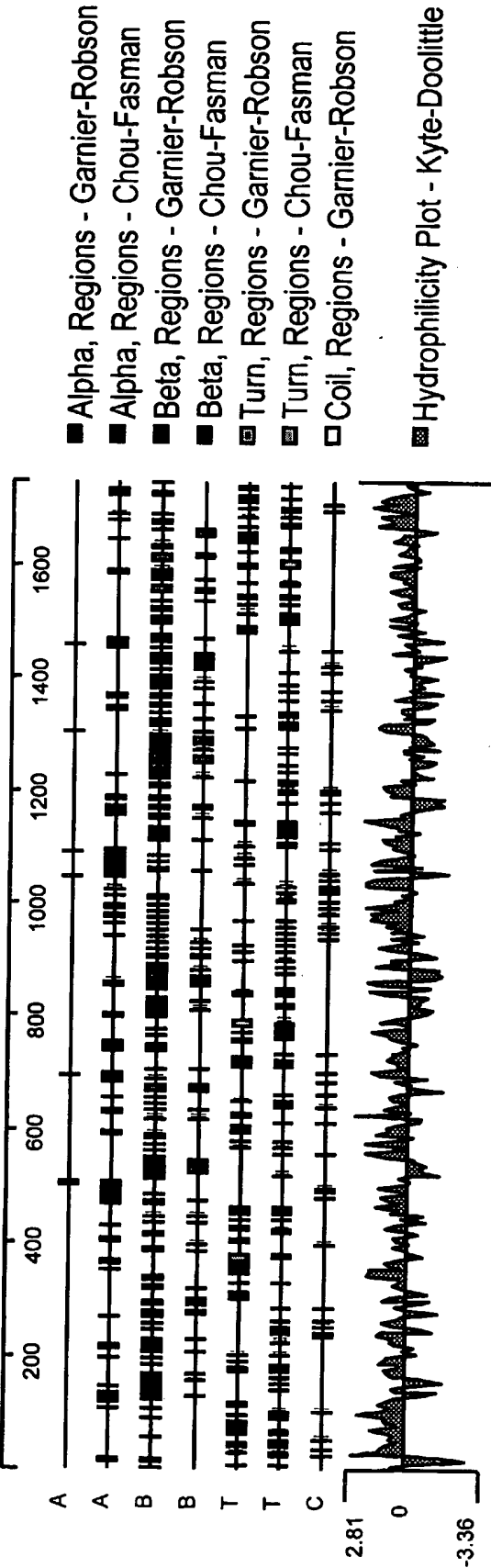


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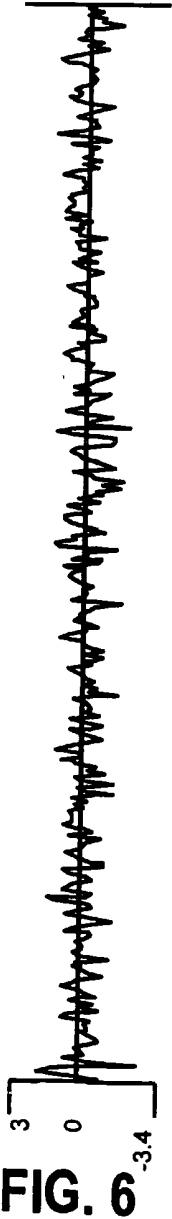
FIG. 5E



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Hydrophobicity Plot - Hopp-Woods



Alpha, Amphipathic Regions - Eisenberg
Beta, Amphipathic Regions - Eisenberg
Flexible Regions - Karplus-Schulz

Antigenic Index - Jameson-Wolf

Surface Probability Plot - Emini

FIG. 6

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1 TGTCCCTTCGTCTCCTTCTTCCCCTAACCAGGCCTCCCTCCACCTGTCTTCTCAGAGCAG 60
61 GTAATGGCAAGCATGGCTGCCGTGCTCACCTGGGCTCTGGCTCTTCTTTTTCAGCGTTTTTCG 120
1 M A S M A A V L T W A L A L L S A F S 19
121 GCCACCCAGGCACGGAAAGGCTTCTGGGACTACTTCAGCCAGACCAGCGGGGACAAAGGC 180
20 A T Q A R K G F W D Y F S Q T S G D K G 39
181 AGGGTGGAGCAGATCCATCAGCAGAAGATGGCTCGCGAGCCCGCGACCCTGAAAGACAGC 240
40 R V E Q I H Q Q K M A R E P A T L K D S 59
241 CTTGAGCAAGACCTCAACAATATGAACAAGTTCCTGGAAAAGCTGAGGCCTCTGAGTGGG 300
60 L E Q D L N N M N K F L E K L R P L S G 79
301 AGCGAGGCTCCTCGGCTCCCACAGGACCCGGTGGGCATGCGGCGGCAGCTGCAGGAGGAG 360
80 S E A P R L P Q D P V G M R R Q L Q E E 99
361 TTGGAGGAGGTGAAGGCTCGCCTCCAGCCCTACATGGCAGAGGCGCACGAGCTGGTGGGC 420
100 L E E V K A R L Q P Y M A E A H E L V G 119
421 TGGAATTTGGAGGGCTTGC GGCAGCAACTGAAGCCCTACACGATGGATCTGATGGAGCAG 480
120 W N L E G L R Q Q L K P Y T M D L M E Q 139
481 GTGGCCCTGCGCGTGCAGGAGCTGCAGGAGCAGTTGCGCGTGGTGGGGGAAGACACCAAG 540
140 V A L R V Q E L Q E Q L R V V G E D T K 159
541 GCCCAGTTGCTGGGGGGCGTGGACGAGGCTTGGGCTTTGCTGCAGGGACTGCAGAGCCGC 600
160 A Q L L G G V D E A W A L L Q G L Q S R 179
601 GTGGTGCACCACACCGCCGCTTCAAAGAGCTCTTCCACCCATACGCCGAGAGCCTGGTG 660
180 V V H H T G R F K E L F H P Y A E S L V 199
661 AGCGGCATCGGGCGCCACGTGCAGGAGCTGCACCGCAGTGTGGCTCCGCACGCCCCCGCC 720

FIG. 7A

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200 S G I G R H V Q E L H R S V A P H A P A 219
.
721 AGCCCCGCGCCTCAGTCGCTGCGTGAGGTGCTCTCCCGGAAGCTCACGCTCAAGGCC 780
220 S P A R L S R C V Q V L S R K L T L K A 239
.
781 AAGGCCCTGCACGCACGCATCCAGCAGAACCTGGACCAGCTGCGCGAAGAGCTTATCAGA 840
240 K A L H A R I Q Q N L D Q L R E E L I R 259
.
841 GCCTTTGCAGGCACTGGGACTGAGGAAGGGGCCGCGCCGACCCCAAGATGCTCTCCGAG 900
260 A F A G T G T E E G A G P D P Q M L S E 279
.
901 GAGGTGCGCCAGCGACTTCAGGCTTTCCGCCAGGACACCTACCTGCAGATAGCTGCCTTC 960
280 E V R Q R L Q A F R Q D T Y L Q I A A F 299
.
961 ACTCGCGCCATCGACCAGGAGACTGAGGAGGTCCAGCAGCAGCTGGCGCCACCTCCACCA 1020
300 T R A I D Q E T E E V Q Q Q L A P P P P 319
.
1021 GGCCACAGTGCCTTCGCCCCAGAGTTTCAACAAACAGACAGTGGCAAGGTTCTGAGCAAG 1080
320 G H S A F A P E F Q Q T D S G K V L S K 339
.
1081 CTGCAGGCCCCTGCTGGATGACCTGTGGGAAGACATCACTCACAGCCTTCATGACCAGGGC 1140
340 L Q A R L D D L W E D I T H S L H D Q G 359
.
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360 H S H L G D P * 367
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1381 AAAAAAAAAAAAAA 1393

FIG. 7B

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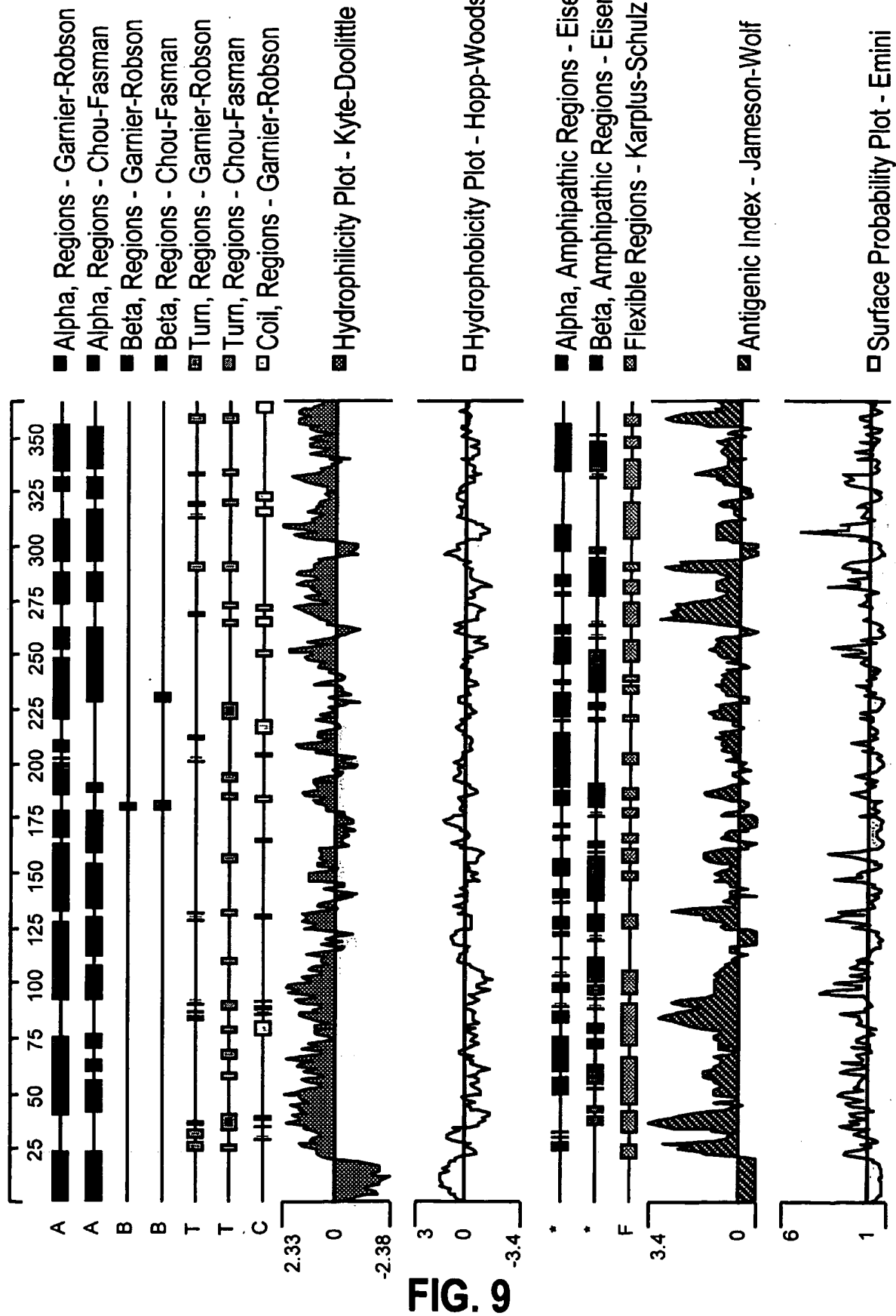
FIG. 8A

		10	20	30	
1	M A S M A A V L T W A L A L L S A - - - F S A T Q A R K G	Apolipoprotein A-IV-Like			
1	M F L K A V V L S L A L V A V T G A R A E V N A D Q V A T V	emb CAA11020.1			
1	M F L K A V V L T L A L V A V A G A R A E V S A D Q V A T V	gb AAA51744.1			
1	M F L K A A V L T L A L V A I T G T R A E V T S D Q V A N V	gb AAA37214.1			
		40	50	60	
27	F W D Y F S Q T S G D - K G R V E Q I H Q Q K M A R E P A T	Apolipoprotein A-IV-Like			
31	M W D Y F S Q L G S N A K K A V E H L Q K S E L T Q Q L N T	emb CAA11020.1			
31	M W D Y F S Q L S N N A K E A V E H L Q K S E L T Q Q L N A	gb AAA51744.1			
31	V W D Y F T Q L S N N A K E A V E Q F Q K T D V T Q Q L S T	gb AAA37214.1			
		70	80	90	
56	L - K D S L E Q D L N N M N K F L E K L R P L S G S E A P R	Apolipoprotein A-IV-Like			
61	L F Q D K L G E V N T Y T E D L Q K K L V P F A T E L H E R	emb CAA11020.1			
61	L F Q D K L G E V N T Y A G D L Q K K L V P F A T E L H E R	gb AAA51744.1			
61	L F Q D K L G D A S T Y A D G V H N K L V P F V V Q L S G H	gb AAA37214.1			
		100	110	120	
85	L P Q D P V G M R R O L Q E E L E E V K A R L Q P Y M A E A	Apolipoprotein A-IV-Like			
91	L T K D S E K L K E E I R R E L E E L R A R L L P H A T E V	emb CAA11020.1			
91	L A K D S E K L K E E I G K E L E E L R A R L L P H A N E V	gb AAA51744.1			
91	L A K E T E R V K E E I K K E L E D L R D R M M P H A N K V	gb AAA37214.1			
		130	140	150	
115	H E L V G W N L E G L R Q Q L K P Y T M D L M E Q V A L R V	Apolipoprotein A-IV-Like			
121	S Q K I G D N V R E L Q Q R L G P F T G G L R T Q V N T Q V	emb CAA11020.1			
121	S Q K I G D N L R E L Q Q R L E P Y A D Q L R T Q V N T Q A	gb AAA51744.1			
121	T Q T F G E N M Q K L Q E H L K P Y A V D L Q D Q I N T Q T	gb AAA37214.1			
		160	170	180	
145	Q E L Q E Q L R V V G E D T K A Q L L G G V D E - - - A W	Apolipoprotein A-IV-Like			
151	Q Q L Q R Q L K P Y A E R M E S V L R Q N I R N L E A S V A	emb CAA11020.1			
151	E Q L R R Q L D P L A Q R M E R V L R E N A D S L Q A S L R	gb AAA51744.1			
151	Q E M K L Q L T P Y I Q R M Q T T I K E N V D N L H T S M M	gb AAA37214.1			
		190	200	210	
171	A L L O G L Q S R V V H H T G R F K E L F H P Y A E S L V S	Apolipoprotein A-IV-Like			
181	P Y A D E F K A K I D Q N V E E L K G S L T P Y A E E L K A	emb CAA11020.1			
181	P H A D E L K A K I D Q N V E E L K G R L T P Y A D E F K V	gb AAA51744.1			
181	P L A T N L K D K F N R N M E E L K G H L T P R A N E L K A	gb AAA37214.1			

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FIG. 8B

		220	230	240	
201	G I G R H V Q E L H R S V A P H A P A S P A R L S R C V Q V				Apolipoprotein A-IV-Like
211	K I D Q N V E E L R R S L A P Y A Q D V Q E K L N H Q L E G				emb CAAl1020.1
211	K I D Q T V E E L R R S L A P Y A Q D T Q E K L N H Q L E G				gb AAA51744.1
211	T I D Q N L E D L R R S L A P L T V G V Q E K L N H Q M E G				gb AAA37214.1
		250	260	270	
231	L S R K L T L K A K A L H A R I Q O N L D O L R E E L I R A				Apolipoprotein A-IV-Like
241	L A F Q M K K Q A E E L K A K I S A N A D E L R Q K L V P V				emb CAAl1020.1
241	L T F Q M K K N A E E L K A R I S A S A E E L R Q R L A P L				gb AAA51744.1
241	L A F Q M K K N A E E L Q T K V S A K I D Q L Q K N L A P L				gb AAA37214.1
		280	290	300	
261	F A G T - - - - G T E E G A G P D P O M L S E E V R Q R L				Apolipoprotein A-IV-Like
271	A E N V H G H L K G N T E G L Q K S L L E L R S H L D Q Q V				emb CAAl1020.1
271	A E D V R G N L K G N T E G L Q K S L A E L G G H L D Q Q V				gb AAA51744.1
271	V E D V Q S K V K G N T E G L Q K S L E D L N R Q L E Q Q V				gb AAA37214.1
		310	320	330	
286	Q A F R Q D T Y L O I A A F T R A I D Q E T E E V Q Q Q L A				Apolipoprotein A-IV-Like
301	E E F R L K V E P Y G E T F N K A L V Q Q V E D L R Q K L G				emb CAAl1020.1
301	E E F R R R V E P Y G E N F N K A L V Q Q M E Q L R Q K L G				gb AAA51744.1
301	E E F R R T V E P M G E M F N K A L V Q Q L E Q F R Q Q L G				gb AAA37214.1
		340	350	360	
316	P P P P G H S A F A P E F Q Q T D S G K V L S K L Q A R L D				Apolipoprotein A-IV-Like
331	P L A G D V E G H L S F L E K D L R D K V N T F F S T L K E				emb CAAl1020.1
331	P H A G D V E G H L S F L E K D L R D K V N S F F S T F K E				gb AAA51744.1
331	P N S G E V E S H L S F L E K S L R E K V N S F M S T L E K				gb AAA37214.1
		370	380	390	
346	D L W E D I T H S L - - - - - H D Q G H S H L G -				Apolipoprotein A-IV-Like
361	E A S Q G Q S Q A L P A Q E K A Q - - - - -				emb CAAl1020.1
361	K E S Q D K T L S L P E L E Q Q Q E Q Q Q E Q Q Q E Q V Q M				gb AAA51744.1
361	K G S P D Q P Q A L P L P E Q A Q E Q A Q E Q V Q P K - - -				gb AAA37214.1
365	- - - - D P				Apolipoprotein A-IV-Like
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<212> DNA

<213> Homo sapiens

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<212> DNA

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<213> Homo sapiens

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<213> Homo sapiens

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<210> 19
 <211> 705
 <212> DNA
 <213> Homo sapiens

<400> 19
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<210> 20
 <211> 2108
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (18)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (34)
 <223> n equals a,t,g, or c

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<210> 21
 <211> 675
 <212> DNA
 <213> Homo sapiens

<400> 21						
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<210> 22
 <211> 1581
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (112)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (959)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1565)
 <223> n equals a,t,g, or c

<400> 22						
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<210> 23
 <211> 922
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (6)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (885)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (886)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (907)
 <223> n equals a,t,g, or c

<400> 23						
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<210> 24
 <211> 2288
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (66)

<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (67)

<223> n equals a,t,g, or c

<400> 24

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<210> 25

<211> 908

<212> DNA

<213> Homo sapiens

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<220>

<221> SITE

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<211> 2090

<212> DNA

<213> Homo sapiens

<400> 26

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<210> 27

<211> 2355
 <212> DNA
 <213> Homo sapiens

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 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (22)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (28)
 <223> n equals a,t,g, or c

<400> 27

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<210> 28
 <211> 1680
 <212> DNA
 <213> Homo sapiens

<400> 28

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<210> 29

<211> 1618

<212> DNA

<213> Homo sapiens

<400> 29

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 <212> DNA
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 <212> DNA
 <213> Homo sapiens

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<211> 2394

<212> DNA

<213> Homo sapiens

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<211> 1365

<212> DNA

<213> Homo sapiens

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<210> 37
 <211> 570
 <212> DNA
 <213> Homo sapiens

<400> 37						
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<210> 38
 <211> 3229
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (3200)
 <223> n equals a,t,g, or c

<400> 38						
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<210> 39

<211> 511

<212> DNA

<213> Homo sapiens

<400> 39

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tcattgtagg	aaagcaattc	tgtacatgag	tttaagcatt	cttgttgcat	tgtctctgca	180
gattctatlt	ttgtttacaa	tattaaaatg	tatgttagca	aaatgggtgg	atltttcaaat	240
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ttcctttctc	tttttattat	caatattgtc	atlttttccc	aataaaatat	acccaggtga	360
ttatatttgt	tgatctaata	acatgggaag	tttgttttat	atgaattttc	aaaaagatgt	420
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<210> 40

<211> 1393

<212> DNA

<213> Homo sapiens

<400> 40

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<210> 41
<211> 1651
<212> DNA
<213> Homo sapiens

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<220>
<221> SITE
<222> (1522)
<223> n equals a,t,g, or c

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<220>
<221> SITE
<222> (1528)
<223> n equals a,t,g, or c

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<220>
<221> SITE
<222> (1540)
<223> n equals a,t,g, or c

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<220>
<221> SITE
<222> (1544)
<223> n equals a,t,g, or c

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<220>
<221> SITE
<222> (1556)
<223> n equals a,t,g, or c

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<220>
<221> SITE
<222> (1572)
<223> n equals a,t,g, or c

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<210> 42
 <211> 1108
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (450)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1108)
 <223> n equals a,t,g, or c

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<210> 43
 <211> 2286
 <212> DNA
 <213> Homo sapiens

<400> 43

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aaaaaa						2286

<210> 44

<211> 1138

<212> DNA

<213> Homo sapiens

<400> 44

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aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa gggcggcc 1138

<210> 45
 <211> 1071
 <212> DNA
 <213> Homo sapiens

<400> 45
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 cttgtgccga gcaccagacg ggaagaaagg ggaggcagga agacctggca gacgggggagc 180
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<210> 46
 <211> 1050
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1026)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1040)
 <223> n equals a,t,g, or c

<400> 46
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 gtgccgagca ccagacggga agaaagggga ggcaggaaga cctggcagac gggggcgggc 240
 aggcmtcaag gsgcttaaa gagaccaggg ggaacctggg ccctctggaa accccggcaa 300
 ggtgggctac ccagggccca gcggccccc cggrgcccg ggcatcccg gaattaaagg 360
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<210> 47

<211> 1149
 <212> DNA
 <213> Homo sapiens

<400> 47
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 aggcacatcatg gaggggtcccc ggggatggct ggtgctctgt gtgctggcca tatcgctggc 180
 ctctatgggtg accgaggact tgtgccgagc accagacggg aagaaagggg aggcaggaag 240
 acctggcaga cggggggcggc caggcctcaa gggggagcaa ggggagccgg gggccccctg 300
 catccggaca ggcacccaag gccttaaagg agaccagggg gaacctgggc cctctggaaa 360
 ccccggaag gtgggctacc cagggccag cggccccctc ggrgcccgtg gcatcccggg 420
 aattaaaggc accaagggca gcccaggaaa catcaaggac cagccgaggc cagccttctc 480
 cgccattcgg cggaaccccc caatgggggg caacgtggtc atcttcgaca cggtcacac 540
 caaccaggaa gaaccgtacc agaaccactc cggccgattc gtctgactg taccgggcta 600
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 tataatgag 1149

<210> 48
 <211> 1086
 <212> DNA
 <213> Homo sapiens

<400> 48
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 atggtgaccg aggacttgtg ccgagcacca gacgggaaga aaggggaggc aggaagacct 180
 ggcagacggg ggcggccagg cctcaagggg gagcaagggg agccgggggc ccctggcatc 240
 cggacaggca tccaaggcct taaaggagac cagggggaac ctgggccctc tggaaccccc 300
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 aaaggcacca agggcagccc aggaacatc aaggaccagc cgaggccagc cttctccgcc 420
 attcggcgga acccccacat ggggggcaac gtggctcatc tcgacacggt catcaccaac 480
 caggaagaac cgtaccagaa cactccggc cgattcgtct gcaactgtacc cggctactac 540
 tacttccact tccaggtgct gtcccagtg gaaatctgcc tgtccatcgt ctctctctca 600
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 gtgggtgtcag ggggcatggt gcttcagctg cagcagggg accaggtctg ggttgaaaaa 720
 gacccccaaa agggctcacat ttaccagggc tctgaggccg acagcgtctt cagcggcttc 780
 ctcatcttcc catctgcctg agccagggaa ggaccccctc cccacccac ctctctggt 840
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 gctctgagag cccaggaact ggctgccccg tgacacatgc tctaagaagc tcgtttctta 960
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 aaaaaaaaaa aaaaaaaaaa aaaaaactcg aggggggggc cggtagccaa ttcgcgctat 1080
 aatgag 1086

<210> 49
 <211> 971
 <212> DNA
 <213> Homo sapiens

<400> 49
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 gctatgggat ggggaatggga gtaaacaagg tacttttyac tttttctttt ttttctcac 180
 tgctagacgg tgtgggaact tctcactcat tggcttcttt cccacacacc tgaagagcac 240
 tgactgtgtg ccgggcacta gtgatacaaa agagtgtgac agttgttcag tctgcatttt 300
 cgatcatggg ctacatgccg agtgctgggg cacagagatg aacaagatcg gttccttcac 360

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aaaaaaaaaa	g					971

<210> 50

<211> 2752

<212> DNA

<213> Homo sapiens

<400> 50

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tctgtatact	gtgaagaagt	tgacattgat	gctgtaccac	ccttaccaa	ggaatcagcc	540
tatctttacg	cacgattcaa	caaaattaaa	aagctgactg	ccaaagattt	tgcagacata	600
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<210> 51
 <211> 2389
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1965)
 <223> n equals a,t,g, or c

<400> 51
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 aacttgccct ctgaatttta catgggtccaa acccgatgaa ttttgtaaaa gaaaatcatg 540
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 gtagaaaata tgcacattaa aaagtgaata ttttaaaatt atgtccttat aagctgaggt 2160
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 tattattatt atttatagtt cttttatagt tcttttatat tttgaatgaa cctctcctta 2280
 gctaaaatag ttatcttgaa agatttgaac agttggattc actttgtttg tttgatattt 2340
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<210> 52
 <211> 2254
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (6)
 <223> n equals a,t,g, or c

<400> 52
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tgatcaagtc	ccagaaaact	ttgccttccc	aaggaatgtg	tttctaattt	ggtttcaaag	240
cacactgggt	cccactttta	ccactttcat	gacattggac	aatagtacta	ctcttttcta	300
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<210> 53

<211> 3559

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (3363)

<223> n equals a,t,g, or c

<400> 53

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<210> 54

<211> 852

<212> DNA

<213> Homo sapiens

<400> 54

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<210> 55
 <211> 609
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (554)
 <223> n equals a,t,g, or c

<400> 55
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<210> 56
 <211> 2099
 <212> DNA
 <213> Homo sapiens

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<210> 57
 <211> 1688
 <212> DNA
 <213> Homo sapiens

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 <222> (21)
 <223> n equals a,t,g, or c

<220>
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 <222> (69)
 <223> n equals a,t,g, or c

<220>
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 <222> (99)
 <223> n equals a,t,g, or c

<400> 57
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<210> 58
 <211> 1354
 <212> DNA
 <213> Homo sapiens

<400> 58
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tagacctatt	cccacttttt	tcacatagta	gtgcgtctgt	tcagagttaa	acaaacaaaa	1320
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<210> 59

<211> 1821

<212> DNA

<213> Homo sapiens

<400> 59

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aaattgaggt	gtatcaatga	ttcggacgag	gagagggtgg	agctcaatgt	ggccatggat	180
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gcagataagt	gaacgagatg	ttctctgtgt	tcagattgct	ggactttgtc	atgatctcgg	300
tcattggcca	ttttctcaca	tgtttgatgg	acgattttatt	ccacttgctc	gcccggagggt	360
gaaatggacg	catgaacaag	gctcagttat	gatgttttag	caccttatta	attctaattg	420
aattaagcct	gtcatggaac	aatatgggtct	catccctgaa	gaagatattt	gctttataaa	480
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aaaaaaaaaa	aaaaaaaaaa	a				1821

<210> 60

<211> 803

<212> DNA

<213> Homo sapiens

<400> 60

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aaagaggttg	ccagtgtctaa	acccaaagta	ttgctagacg	tgaaactgaa	ggctgaagat	120
tttatagtgg	atgtttatcaa	catggattat	ggaatgcaag	aaaagaatcc	aattgatcat	180
gttagcttct	attgtaagac	tgccccaac	agagcaatca	ggattactaa	aaaccagggt	240
tcacaacttc	tgccagagaa	atttgcagag	cagctgattc	gagtatattg	taagaagggtg	300
gacagaaaaga	gtttgtatgc	cgcaagacaa	tattttgttc	agtgggtgtg	agacagaaat	360
ttcaccaagc	cgcaggatgg	cgatgttata	gccccactca	taacacctca	aaaaaaggaa	420
tggaacgaca	gtacttcagt	ccaaaatcca	actcgctctc	gagaagcatc	caaaagcaga	480
gtccagcttt	ttaaagatga	cccaatgtga	atgtctgtag	tcagttgttt	acaaactccc	540
tctcctgcac	aattcattta	gaggcttcaa	tcatagaatt	ctgcaaatta	atgacaactc	600
atgctttaat	tttgtatttt	gaatgtacac	gcattgctgaa	gctaagtaac	ttttaatcaa	660
agaaataaga	tggtattagg	caaactctac	tatactatga	aaagcattac	cttgcctatt	720
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<210> 61

<211> 1499

<212> DNA

<213> Homo sapiens

<400> 61

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gtgtcagcgc	ggggagggtg	gggggtattt	atctatttat	acatgggatt	gtacatagtc	180
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ccccactccc	cacccccctg	ctgtgactgc	tgtaagatgg	gggtatagag	gctgggcaat	480
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agacccaagc	tacaaggttg	gaatttttgt	tggttttttt	tttaagtacc	ctgcctgtat	1320
aattgcatca	gaatccccca	ccccaccccc	cgcctcctgt	tttgtatttt	gggttgggtt	1380
acactcgcac	atactcagtt	ttcagttttc	ccctttacag	tcttctcccc	tcacctccag	1440
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<210> 62

<211> 974

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (563)

<223> n equals a,t,g, or c

<400> 62

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gctgggtaag	gacttccagg	gaccctctgt	gacttcccaa	ctttccccag	ccctgaccct	420
gctcactgtc	agcgcccttc	cctcccacag	gcacccaccg	cccccttgcc	cgcytgcgcc	480
gagccctgtc	tgggtccatgc	cagctgtgga	gcctgaccct	gtccgtggca	gagctaggcc	540
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cctggcaccc	agaagctgca	gtgctggggg	agctcggctg	acttatattat	tggagacctg	840
gatgcagaga	caacgaggag	gggagtgggc	tggggcgacc	agcagtgagt	gcaataaagg	900
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<210> 63
 <211> 872
 <212> DNA
 <213> Homo sapiens

<400> 63	
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aactcaatca	ttgtggacct
gatgtatttc	ccaatcaacc
gctatttttg	atacaccaga
ggaggcttcg	cctgggggtga
gagaccagc	tgggaaggac
agtgtggaca	cttttgacag
acactgacta	atccagaaga
actgaaagt	taatttctta
acaagtacat	gagtacttga
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	aa

<210> 64
 <211> 1208
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1038)
 <223> n equals a,t,g, or c

<220>
 <221> SITE
 <222> (1148)
 <223> n equals a,t,g, or c

<400> 64	
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gatcccaccg	gtcagccgcg
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tcaaataatg	agattaatca
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tgggacagca	gactttgtat
tctgtttgtg	agcttagttt
gagccgaagg	aaccctatg
ctttctgccc	tgggtgctca
ccttttgggt	attgcagttg
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agatgaggat	ccaaattaca
tgagggccag	cggtctggag
gactcgggtga	taccacttgg
	gatcttttat
	cctttgttgc
	aaaagtgtgg
	acacttttga

cagcttggca	gattttaact	ccagaagcac	tttatgaaat	ggtacactga	ctaataccaga	900
agacatttcc	aacagtttgc	cagtggttcc	tcactacact	ggtactgaaa	gtgtaatttc	960
ttagagccaa	aaaactggag	aaacaaatat	cctgccacct	ctaacaagta	catgagtact	1020
tgatttttat	ggtataangc	agagcctttt	cttcctcttc	ttgatagatg	aggccatggt	1080
gtaaatggaa	gtttcagaga	ggacaaaata	aaacggaatt	ccatttttct	ctcactgtaa	1140
aagctttngt	gtgtgatctt	ttaaattctg	ataatgtatt	gtaaccctcc	tgcgtagatc	1200
tgagctca						1208

<210> 65
 <211> 1167
 <212> DNA
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (432)
 <223> n equals a,t,g, or c

<400> 65						
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gcagttggaa	ttgatcacac	cttttcagtt	gtacttcaat	cctgaattaa	tctttaaaca	180
ctttcaata	tgagattaa	tcaccaactt	cttatttttt	gggccagttg	gattcaattt	240
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aaggactcgg	tgataccac	tgggatcttt	tatcctttgt	tgcaaaagtg	tggacacttt	840
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aaaaaaaaaa	aaaaaaaggg	cggccgc				1167

<210> 66
 <211> 2311
 <212> DNA
 <213> Homo sapiens

<400> 66						
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aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	a			2311

<210> 67

<211> 1049

<212> DNA

<213> Homo sapiens

<400> 67

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ccaactcctc	caactccagc	gccaagaacc	atgccgccta	ctaagcccca	gccccagcc	180
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<210> 68

<211> 3299

<212> DNA

<213> Homo sapiens

<400> 68

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ccgcgggtctg	tttggcccga	acggcggcgg	aggcgctgat	catggcgaca	ttcatctcgg	180
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<210> 69

<211> 1772

<212> DNA

<213> Homo sapiens

<400> 69

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<210> 70

<211> 1121

<212> DNA

<213> Homo sapiens

<400> 70

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<210> 71

<211> 938

<212> DNA

<213> Homo sapiens

<400> 71

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938

<210> 72
 <211> 943
 <212> DNA
 <213> Homo sapiens

<400> 72
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<210> 73
 <211> 1810
 <212> DNA
 <213> Homo sapiens

<220>
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 <222> (1803)
 <223> n equals a,t,g, or c

<400> 73
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<210> 74

<211> 1543

<212> DNA

<213> Homo sapiens

<400> 74

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<210> 75

<211> 1806

<212> DNA

<213> Homo sapiens

<400> 75

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ctttgcctgc	tgtcagagga	gcagctatct	gattggaaac	ctgccgactt	agtgcggtga	1560
taggaagcta	aaagtgtcaa	gcgttgacag	cttgggaagcg	tttatttata	catctctgta	1620
aaaggatatt	ttagaattga	gttgtgtgaa	gatgtcaaaa	aaagatttta	gaagtgcatt	1680
atttatagtg	ttatttgttt	caccttcaag	ccttttgccct	gaggtgttac	aatcttgtct	1740
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ctcgag						1806

<210> 76

<211> 1547

<212> DNA

<213> Homo sapiens

<400> 76

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tcctctagcc	aaggcaagcc	atgaaggact	gtgccgtgag	ggacggtgct	atctgaccca	180
catactacgc	ttttccgatg	gttttcacaa	cccacagacc	aaaagattcc	cttgggtgcc	240
tatacaacca	gggccctggg	tatcaagcat	aaaactggat	ggccgtttgg	ggagacaccg	300
agctggctgc	aggagttttt	tgtttttttt	tgtttttttg	ttttttgtac	ctcagtggca	360
cctggaatgc	cagcaagaca	gaactgttca	ctcctctgga	aagggagctg	aagccagggc	420
acccgagtgg	tatgctcagc	ggatcccacc	cccacggagc	ccaacaagct	aaatccactg	480
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tgtggggagg	ggcatctgcc	attactgagg	ctttgtaaac	aaagctgaca	gaaagtgtga	600
actgggtgca	gaaccaaca	cagcatggca	aagccgctgt	agccagaatc	tagagaggca	660
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ggagcttata	gaaaaaactc	ccatgtccct	gggacagagc	acctggggga	aggggcagct	780
gtgggcacag	cttcaacaga	cttaaacctt	cctgcctgct	ggctctgaag	agaggaacag	840
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tgacccccgt	gcctctgact	gggagacacc	ttccagcagg	ggacgacaga	cacctcaaac	960
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aaccccatcc	aaaggtcacc	aacatcaaac	accaaaggta	gataaattca	cgaagatgag	1260
gaaaaaccaa	cgcaaaaagg	ctgaaaattc	ccaaaaccag	aatgcctctt	ctcctccaaa	1320
gtatcacaac	tccttgccag	taagggaaca	aaactggacg	gagaatgagt	ttgatgaatt	1380
gacagaagta	ggcttcagaa	ggtgggtaat	aacaaactct	caagctaaag	gagtgtgttt	1440
taacccaatg	caaggaagct	aagaaccttg	ataaaaagtt	acaggaacta	tcactagaat	1500
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<210> 77

<211> 1811

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (1804)

<223> n equals a,t,g, or c

<400> 77

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cctgcacttg	gtctgcgtgg	acatgccagg	acatgagggc	accacccgct	cctccctgga	120
tgacctgtcc	atagatgggg	aagttaagag	gatacaccag	tttgtagaat	gcctgaagct	180
gaacaaaaaa	cctttccacc	tggtaggcac	ctccatgggt	ggccaggtgg	ctgggggtga	240
tgtcgcttac	taccctcgg	atgtctccag	cctgtgtctc	gtgtgtcctg	ctggcctgca	300
gtactcaact	gacaatcaat	ttgtacaacg	gctcaaagaa	ctgcagggct	ctgcgcctg	360
ggagaagatt	cccttgatcc	cgtctacccc	agaagagatg	agtgaatgc	ttcagctctg	420
ctcctatgtc	cgcttcaagg	tgccccagca	gatectgcaa	ggccttgtcg	atgtccgcac	480
ccctcataac	aacttctacc	gaaagttggt	tttggaatc	gtcagtgaga	agtccagata	540

ctctctccat	cagaacatgg	acaagatcaa	ggttccgacg	cagatcatct	gggggaaaca	600
agacgcaggt	gctggatgtg	tctggggcag	acatggttggc	caagtcaatt	gccaactgcc	660
aggtggagct	tctggaaaac	tgtggggcact	cagtagtgat	ggaaagaccc	aggaagacag	720
ccaagctcat	aatcgacttt	ttagcttctg	tgcacaacac	agacaacaac	aagaagctgg	780
actgaggccc	cgactgcagc	ctgcattctg	cacacagcat	ctgctcccat	cccccaagtc	840
tgacgcagcc	accactctca	gggatcctgc	cccaaattgcg	gtcggagcgc	cagtgaccct	900
gaggaagccc	gtcccttata	cctggatatcc	acggttcccc	agagctttgg	ggaccacgcg	960
aaaacctcca	agatattttt	cacaaaatag	aaactcatat	ggaacaaaat	aagaaacccc	1020
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gccaccttgg	accataatta	aatcaaggac	atthttctttg	agacattcct	tatagttgga	1140
gactcaagat	atthttgttg	catcaggtgt	attcccttgc	atgggcagtg	gctthttatag	1200
gagcattagt	cctcatctgc	tgaacctgt	tgttttaggtc	taatttaagt	tttacaataga	1260
gacccatgta	tgactgcagc	ccattggctg	caagaccagg	gaggaaagtg	gcaagctgta	1320
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grtacatggg	tgggaggttc	attcagcacc	caccagtcag	gtatgttctg	agtgaaccca	1440
cagcagtcgc	agaatgagca	cctggcaggg	tgggtttcct	aggaataatt	tattatthttt	1500
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ttccacacac	aagcaacaac	tcgtgggcct	ctthttctatt	tcaatgtgct	actaagaacc	1620
cttggaatgta	acatactagt	tagttaatga	attctgtgaa	ttctgtgaag	agtaatgtga	1680
ttgaaataa	gtctaaacag	ctgtaaaagt	gaccacaatg	acatgaaata	aatttaataa	1740
gtctagatca	gcaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1800
aaanaaaaaa	a					1811

<210> 78

<211> 1141

<212> DNA

<213> Homo sapiens

<400> 78

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ctgtgccagg	ccagaaaccg	cccacctgca	gttccttctc	cgggatggac	gtggggccca	120
gtccctgcc	ccaccttggg	ctgaagctgc	tgtgtctcct	gctgtctgctg	cccctcaggg	180
gccaagccaa	cacaggctgc	tacgggatcc	cagggatgcc	cggcctgccc	ggggcaccag	240
ggaaggatgg	gtacgacgga	ctgccggggc	ccaaggggga	gccaggaatc	ccagccattc	300
ccgggatccg	aggaccaaag	ggcagatata	agcagaaatt	ccagtcagtg	ttcacggtca	360
ctcggcagac	ccaccagccc	cctgcaccca	acagcctgat	cagattcaac	gcggtcctca	420
ccaacctgca	gggagattat	gacacgagca	ctggcaagtt	cacctgcaaa	gtccccggcc	480
tctactactt	tgtctaccac	gcgtcgcata	cagccaacct	gtgcgtgctg	ctgtaccgca	540
gcggcgctca	agtggtcacc	ttctgtggcc	acacgtccaa	aaccaatcag	gtcaactcgg	600
gcggtgtgct	gctgaggttg	caggtggggc	aggaggtgtg	gctggctgtc	aatgactact	660
acgacatgg	gggcatccag	ggctctgaca	gcgtcttctc	cggcttctctg	ctcttccccg	720
actagggcgg	gcagatgcgc	tcgagcccca	cgggccttcc	acctccctca	gcttctctgca	780
tggacccacc	ttactggcca	gtctgcaccc	ttgcctagac	cattctcccc	accagatgga	840
cttctcctcc	agggagccca	ccctgaccca	ccccactgc	acccccctcc	catgggttct	900
ctccttctct	tgaacttctt	taggagtcac	tgtttgtgtg	gttctctggga	cacttaacca	960
atgccttctg	gtactgccat	tctthttttt	thttthttcaa	gtatttggaa	gggtggggag	1020
atatataaat	aaatcatgaa	atcaatacat	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1080
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1140
a						1141

<210> 79

<211> 990

<212> DNA

<213> Homo sapiens

<220>

<221> SITE

<222> (908)

<223> n equals a,t,g, or c

<400> 79

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cagatgcgac	atccagctga	cccagctctc	atcctccctg	tctgcatctc	ttggcgacag	120
cgtcaccatc	acttgccagg	cgagtcagga	catcgccaac	tatttgaatt	ggtatcagca	180

gaagccccggg	aaacccccca	aactcgtgat	cttcgatgga	tctattttac	atacaggggt	240
cccatcaagg	ttcagtgagg	gtggatctgg	gacacatttc	actttcacca	tcaacaacct	300
gcagcctgac	gatgttgcaa	catattcctg	tcaacartat	aatactttcc	ccctcacktt	360
cggcsraggg	accaaggtgg	aratcaaagc	aactgtggct	gcaccatctg	tcttcattct	420
cccgccatct	gatgagcagt	tgaatcttgg	aactgcctct	gttgtgtgcc	tgctgaataa	480
cttctatccc	agagaggcca	aagtacagtg	gaaggtggat	aacgccctcc	aatcgggtaa	540
ctcccaggag	agtgtcacag	agcaggacag	caaggacagc	acctacagcc	tcagcagcac	600
cctgacgctg	agcaaagcag	actacgagaa	acacaaagtc	tacgcctgcg	aagtcaccca	660
tcagggcctg	agctcgcccg	tcacaaagag	cttcaacagg	ggagagtgtt	agagggagaa	720
gtgccccac	ctgctcctca	gttccagcct	gaccccctcc	catcctttgg	cctctgaccc	780
tttttccaca	ggggacctac	ccctattgctg	gtcctccagc	tcctctttca	cctcaccccc	840
ctcctcctcc	ttggctttta	ttatgcta	gttggaggag	aatgaataaa	taaagtgaat	900
ctttgcanaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	960
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa				990

<210> 80

<211> 1297

<212> DNA

<213> Homo sapiens

<400> 80

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agcagatctg	aggacatctc	tgtgccaggc	cagaaaaccgc	ccacctgcag	tccctctccc	180
gggatggacg	tggggcccag	ctccctgccc	caccttgggc	tgaagctgct	gctgctcctg	240
ctgctgctgc	ccctcagggg	ccaagccaac	acaggctgct	acgggatccc	agggatgccc	300
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ccaggaatcc	cagccattcc	cgggatccga	ggacccaaag	ggcagaaggg	agaaccgggc	420
ttacccggcc	atcctgggaa	aaatggcccc	atgggacccc	ctgggatgcc	aggggtgccc	480
ggcccatgg	gcatccctgg	agagccaggt	gaggagggca	gatacaagca	gaaattccag	540
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ttcaacgcgg	tcctcaccaa	cccgcaggag	attatgacac	gagcactggc	aagttcacct	660
gcaaagtccc	cggcctctac	tactttgtct	accacgcgtc	gcatacagcc	aacctgtgctg	720
tgctgctgta	ccgcagcggc	gtcaaagtgg	tcaccttctg	tggccacacg	tccaaaacca	780
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tcctgctctt	ccccgactag	ggcgggcaga	tgcgctcgag	acccacgggc	cttccacctc	960
cctcagcttc	ctgcatggac	ccaccttact	ggccagtctg	catccttgcc	tagaccattc	1020
tccctccag	ggagcccacc	ctgacccacc	cccactgcac	cccctcccca	tgggttctct	1080
ccttctctg	aacttcttta	ggagtcactg	cttgtgtggt	tcctgggaca	cttaaccaat	1140
gccttctggt	actgccattc	tttttttttt	tttttcaagt	attggaaggg	gtggggagat	1200
atataaataa	atcatgaaat	caaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	1260
aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aaaaaaa			1297

<210> 81

<211> 941

<212> DNA

<213> Homo sapiens

<400> 81

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tctgttggag	acagagtcac	catcacttgc	ggcagaagtc	agagcattgg	caaattttta	180
aattgggtatc	aacaaaaacc	agggcaagcc	cctaagctcc	tgatctctgg	tgcatccatt	240
ttgcaaactg	gggtcccctc	aagattcagt	ggcagtggat	ctgccacata	tttactctc	300
accatcaatg	acctacaccc	tgaagattct	gcaacttatt	actgtcaaca	ggattacact	360
accccccttt	tcggccaagg	gaccaaggtt	gaaatcaagc	gaactgtggc	tgaccatct	420
gtcttcatct	tcccgcctatc	tgatgagcag	ttgaaatctg	gaactgcctc	tggtgtgtgc	480
ctgctgaata	acttctatcc	cagagaggcc	aaagtacagt	ggaagggtga	taacgcctc	540
caatcgggta	actcccagga	gagtgtcaca	gagcaggaga	gcaaggacag	cacctacagc	600
ctcagcagca	ccctgacgct	gagcaaagca	gactacgaga	aacacaaagt	ctacgcctgc	660
gaagtcaccc	atcagggcct	gagctcgccc	gtcacaaga	gcttcaacag	gggagagtgt	720
tagagggaga	agtgccecca	cctgctcctc	agttccagcc	tgacccccctc	ccatcctttg	780
gcctctgacc	ctttttccac	aggggaccta	cccctattgc	ggctcctccag	ctcatctttc	840

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ataaagtga tctttgcacc tgtaaaaaaa aaaaaaaaaa a 941

<210> 82
<211> 613
<212> PRT
<213> Homo sapiens

<400> 82
Met Gly Ala Leu Arg Pro Thr Leu Leu Pro Pro Ser Leu Pro Leu Leu
1 5 10 15
Leu Leu Leu Met Leu Gly Met Gly Cys Trp Ala Arg Glu Val Leu Val
20 25 30
Pro Glu Gly Pro Leu Tyr Arg Val Ala Gly Thr Ala Val Ser Ile Ser
35 40 45
Cys Asn Val Thr Gly Tyr Glu Gly Pro Ala Gln Gln Asn Phe Glu Trp
50 55 60
Phe Leu Tyr Arg Pro Glu Ala Pro Asp Thr Ala Leu Gly Ile Val Ser
65 70 75 80
Thr Lys Asp Thr Gln Phe Ser Tyr Ala Val Phe Lys Ser Arg Val Val
85 90 95
Ala Gly Glu Val Gln Val Gln Arg Leu Gln Gly Asp Ala Val Val Leu
100 105 110
Lys Ile Ala Arg Leu Gln Ala Gln Asp Ala Gly Ile Tyr Glu Cys His
115 120 125
Thr Pro Ser Thr Asp Thr Arg Tyr Leu Gly Ser Tyr Ser Gly Lys Val
130 135 140
Glu Leu Arg Val Leu Pro Asp Val Leu Gln Val Ser Ala Ala Pro Pro
145 150 155 160
Gly Pro Arg Gly Arg Gln Ala Pro Thr Ser Pro Pro Arg Met Thr Val
165 170 175
His Glu Gly Gln Glu Leu Ala Leu Gly Cys Leu Ala Arg Thr Ser Thr
180 185 190
Gln Lys His Thr His Leu Ala Val Ser Phe Gly Arg Ser Val Pro Glu
195 200 205
Ala Pro Val Gly Arg Ser Thr Leu Gln Glu Val Val Gly Ile Arg Ser
210 215 220
Asp Leu Ala Val Glu Ala Gly Ala Pro Tyr Ala Glu Arg Leu Ala Ala
225 230 235 240
Gly Glu Leu Arg Leu Gly Lys Glu Gly Thr Asp Arg Tyr Arg Met Val
245 250 255
Val Gly Gly Ala Gln Ala Gly Asp Ala Gly Thr Tyr His Cys Thr Ala
260 265 270
Ala Glu Trp Ile Gln Asp Pro Asp Gly Ser Trp Ala Gln Ile Ala Glu
275 280 285
Lys Arg Ala Val Leu Ala His Val Asp Val Gln Thr Leu Ser Ser Gln
290 295 300

Leu Ala Val Thr Val Gly Pro Gly Glu Arg Arg Ile Gly Pro Gly Glu
 305 310 315 320
 Pro Leu Glu Leu Leu Cys Asn Val Ser Gly Ala Leu Pro Pro Ala Gly
 325 330 335
 Arg His Ala Ala Tyr Ser Val Gly Trp Glu Met Ala Pro Ala Gly Ala
 340 345 350
 Pro Gly Pro Gly Arg Leu Val Ala Gln Leu Asp Thr Glu Gly Val Gly
 355 360 365
 Ser Leu Gly Pro Gly Tyr Glu Gly Arg His Ile Ala Met Glu Lys Val
 370 375 380
 Ala Ser Arg Thr Tyr Arg Leu Arg Leu Glu Ala Ala Arg Pro Gly Asp
 385 390 395 400
 Ala Gly Thr Tyr Arg Cys Leu Ala Lys Ala Tyr Val Arg Gly Ser Gly
 405 410 415
 Thr Arg Leu Arg Glu Ala Ala Ser Ala Arg Ser Arg Pro Leu Pro Val
 420 425 430
 His Val Arg Glu Glu Gly Val Val Leu Glu Ala Val Ala Trp Leu Ala
 435 440 445
 Gly Gly Thr Val Tyr Arg Gly Glu Thr Ala Ser Leu Leu Cys Asn Ile
 450 455 460
 Ser Val Arg Gly Gly Pro Pro Gly Leu Arg Leu Ala Ala Ser Trp Trp
 465 470 475 480
 Val Glu Arg Pro Glu Asp Gly Glu Leu Ser Ser Val Pro Ala Gln Leu
 485 490 495
 Val Gly Gly Val Gly Gln Asp Gly Val Ala Glu Leu Gly Val Arg Pro
 500 505 510
 Gly Gly Gly Pro Val Ser Val Glu Leu Val Gly Pro Arg Ser His Arg
 515 520 525
 Leu Arg Leu His Ser Leu Gly Pro Glu Asp Glu Gly Val Tyr His Cys
 530 535 540
 Ala Pro Ser Ala Trp Val Gln His Ala Asp Tyr Ser Trp Tyr Gln Ala
 545 550 555 560
 Gly Ser Ala Arg Ser Gly Pro Val Thr Val Tyr Pro Tyr Met His Ala
 565 570 575
 Leu Asp Thr Leu Phe Val Pro Leu Leu Val Gly Thr Gly Val Ala Leu
 580 585 590
 Val Thr Gly Ala Thr Val Leu Gly Thr Ile Thr Cys Cys Phe Met Lys
 595 600 605
 Arg Leu Arg Lys Arg
 610

<210> 83
 <211> 453
 <212> PRT
 <213> Homo sapiens

<400> 83

Met Lys Leu Leu Val Ile Leu Ile Phe Ser Gly Leu Ile Thr Cys Cys
 1 5 10 15
 Gly Gly Asn Ser Ser His Ser Leu Pro Ser Lys Leu Leu Leu Val Ser
 20 25 30
 Phe Asp Gly Phe Arg Ala Asp Tyr Leu Gln Asn Tyr Glu Phe Pro His
 35 40 45
 Leu Gln Asn Phe Ile Lys Glu Gly Val Leu Val Glu His Val Lys Asn
 50 55 60
 Val Phe Ile Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly
 65 70 75 80
 Leu Tyr Glu Glu Ser His Gly Ile Val Ala Asn Ser Met Tyr Asp Val
 85 90 95
 Ile Thr Lys Lys His Phe Ser Asp Phe Asp Asp Lys Asp Pro Phe Trp
 100 105 110
 Trp Asn Glu Ala Val Pro Ile Trp Val Thr Asn Gln Leu Gln Glu Asn
 115 120 125
 Arg Ser Ser Ala Ala Ala Met Trp Pro Gly Thr Asp Val Pro Ile His
 130 135 140
 Asn Thr Thr Pro Ser Tyr Phe Met Asn Tyr Ser Ser Ser Val Ser Phe
 145 150 155 160
 Glu Glu Arg Leu Asn Asn Ile Thr Met Trp Leu Met Asn Ser Asn Pro
 165 170 175
 Pro Val Thr Phe Ala Thr Leu Tyr Trp Glu Glu Pro Asp Ala Ser Gly
 180 185 190
 His Lys Tyr Gly Pro Glu Asp Lys Glu Asn Met Tyr Arg Val Leu Lys
 195 200 205
 Glu Val Asp Asp Leu Ile Gly Glu Leu Val His Lys Leu Lys Val Leu
 210 215 220
 Gly Leu Trp Glu Asn Leu Asn Val Ile Ile Thr Ser Asp His Gly Met
 225 230 235 240
 Thr Gln Cys Ser Lys Asp Lys Leu Ile Asn Leu Asp Leu Cys Ile Asp
 245 250 255
 Arg Ser Ser Tyr Thr Leu Val Asp Leu Thr Pro Val Ala Ala Val Leu
 260 265 270
 Pro Lys Ile Asn Thr Thr Glu Val Tyr Asn Lys Leu Lys Val Cys Asn
 275 280 285
 Pro His Met Asn Val Tyr Leu Lys Glu Asp Ile Pro Ala Arg Phe His
 290 295 300
 Tyr Gln His Asn Asp Arg Ile Gln Pro Ile Ile Leu Val Ala Asp Glu
 305 310 315 320
 Gly Trp Thr Ile Val Leu Asn Lys Ser Leu Pro Lys Leu Gly Asp His
 325 330 335
 Gly Tyr Asp Asn Ser Leu Ser Ser Met His Pro Phe Leu Ala Ala His

[illegible]

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<210> 84
<211> 152
<212> PRT
<213> Homo sapiens
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[illegible]

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<210> 85
<211> 245
<212> PRT
<213> Homo sapiens
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50

<400> 85

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 1 5 10 15

Leu Ala Ser Met Val Thr Glu Asp Leu Cys Arg Ala Pro Asp Gly Lys
 20 25 30

Lys Gly Glu Ala Gly Arg Pro Gly Arg Arg Gly Arg Pro Gly Leu Lys
 35 40 45

Gly Glu Gln Gly Glu Pro Gly Ala Pro Gly Ile Arg Thr Gly Ile Gln
 50 55 60

Gly Leu Lys Gly Asp Gln Gly Glu Pro Gly Pro Ser Gly Asn Pro Gly
 65 70 75 80

Lys Val Gly Tyr Pro Gly Pro Ser Gly Pro Leu Gly Ala Arg Gly Ile
 85 90 95

Pro Gly Ile Lys Gly Thr Lys Gly Ser Pro Gly Asn Ile Lys Asp Gln
 100 105 110

Pro Arg Pro Ala Phe Ser Ala Ile Arg Arg Asn Pro Pro Met Gly Gly
 115 120 125

Asn Val Val Ile Phe Asp Thr Val Ile Thr Asn Gln Glu Glu Pro Tyr
 130 135 140

Gln Asn His Ser Gly Arg Phe Val Cys Thr Val Pro Gly Tyr Tyr Tyr
 145 150 155 160

Phe Thr Phe Gln Val Leu Ser Gln Trp Glu Ile Cys Leu Ser Ile Val
 165 170 175

Ser Ser Ser Arg Gly Gln Val Arg Arg Ser Leu Gly Phe Cys Asp Thr
 180 185 190

Thr Asn Lys Gly Leu Phe Gln Val Val Ser Gly Gly Met Val Leu Gln
 195 200 205

Leu Gln Gln Gly Asp Gln Val Trp Val Glu Lys Asp Pro Lys Lys Gly
 210 215 220

His Ile Tyr Gln Gly Ser Glu Ala Asp Ser Val Phe Ser Gly Phe Leu
 225 230 235 240

Ile Phe Pro Ser Ala
 245

<210> 86

<211> 396

<212> PRT

<213> Homo sapiens

<400> 86

Met Trp Trp Leu Leu Leu Trp Gly Val Leu Gln Ala Cys Pro Thr Arg
 1 5 10 15

Gly Ser Val Leu Leu Ala Gln Glu Leu Pro Gln Gln Leu Thr Ser Pro
 20 25 30

Gly Tyr Pro Glu Pro Tyr Gly Lys Gly Gln Glu Ser Ser Thr Asp Ile
 35 40 45

Lys Ala Pro Glu Gly Phe Ala Val Arg Leu Val Phe Gln Asp Phe Asp

50					55					60					
Leu 65	Glu	Pro	Ser	Gln	Asp 70	Cys	Ala	Gly	Asp	Ser 75	Val	Thr	Ile	Ser	Phe 80
Val	Gly	Ser	Asp	Pro 85	Ser	Gln	Phe	Cys	Gly 90	Gln	Gln	Gly	Ser	Pro	Leu 95
Gly	Arg	Pro	Pro 100	Gly	Gln	Arg	Glu	Phe 105	Val	Ser	Ser	Gly	Arg	Ser	Leu 110
Arg	Leu	Thr 115	Phe	Arg	Thr	Gln	Pro 120	Ser	Ser	Glu	Asn	Lys 125	Thr	Ala	His
Leu 130	His	Lys	Gly	Phe	Leu	Ala 135	Leu	Tyr	Gln	Thr	Val 140	Ala	Val	Asn	Tyr
Ser 145	Gln	Pro	Ile	Ser	Glu 150	Ala	Ser	Arg	Gly	Ser 155	Glu	Ala	Ile	Asn	Ala 160
Pro	Gly	Asp	Asn 165	Pro	Ala	Lys	Val	Gln	Asn 170	His	Cys	Gln	Glu	Pro	Tyr 175
Tyr	Gln	Ala	Ala 180	Ala	Ala	Gly	Ala	Leu 185	Thr	Cys	Ala	Thr	Pro	Gly	Thr 190
Trp	Lys	Asp 195	Arg	Gln	Asp	Gly	Glu 200	Glu	Val	Leu	Gln	Cys 205	Met	Pro	Val
Cys 210	Gly	Arg	Pro	Val	Thr	Pro 215	Ile	Ala	Gln	Asn	Gln 220	Thr	Thr	Leu	Gly
Ser 225	Ser	Arg	Ala	Lys	Leu 230	Gly	Asn	Phe	Pro	Trp 235	Gln	Ala	Phe	Thr	Ser 240
Ile	His	Gly	Arg	Gly 245	Gly	Gly	Ala	Leu	Leu 250	Gly	Asp	Arg	Trp	Ile	Leu 255
Thr	Ala	Ala	His 260	Thr	Ile	Tyr	Pro	Lys 265	Asp	Ser	Val	Ser	Leu	Arg	Lys 270
Asn	Gln	Ser 275	Val	Asn	Val	Phe	Leu 280	Gly	His	Thr	Ala	Ile 285	Asp	Glu	Met
Leu 290	Lys	Leu	Gly	Asn	His	Pro 295	Val	His	Arg	Val	Val	Val	His	Pro	Asp 300
Tyr 305	Arg	Gln	Asn	Glu	Ser 310	His	Asn	Phe	Ser	Gly 315	Asp	Ile	Ala	Leu	Leu 320
Glu	Leu	Gln	His	Ser 325	Ile	Pro	Leu	Gly	Pro 330	Asn	Val	Leu	Pro	Val	Cys 335
Leu	Pro	Asp	Asn 340	Glu	Thr	Leu	Tyr	Arg 345	Ser	Gly	Leu	Leu	Gly	Tyr	Val 350
Ser	Gly	Phe 355	Gly	Met	Glu	Met	Gly 360	Trp	Leu	Thr	Thr	Glu 365	Leu	Lys	Tyr
Ser 370	Arg	Leu	Pro	Val	Ala	Pro 375	Arg	Glu	Ala	Cys	Asn 380	Ala	Trp	Leu	Gln
Lys 385	Arg	Gln	Arg	Pro	Glu 390	Lys	Lys	Lys	Lys	Lys	Lys 395	Lys	Lys	Lys	Lys

52

<210> 87

<211> 298

<212> PRT

<213> Homo sapiens

<400> 87

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Met Lys Thr Leu Gln Ser Thr Leu Leu Leu Leu Leu Val Pro Leu
 1          5          10          15
Ile Lys Pro Ala Pro Pro Thr Gln Gln Asp Ser Arg Ile Ile Tyr Asp
          20          25          30
Tyr Gly Thr Asp Asn Phe Glu Glu Ser Ile Phe Ser Gln Asp Tyr Glu
          35          40          45
Asp Lys Tyr Leu Asp Gly Lys Asn Ile Lys Glu Lys Glu Thr Val Ile
          50          55          60
Ile Pro Asn Glu Lys Ser Leu Gln Leu Gln Lys Asp Glu Ala Ile Thr
          65          70          75          80
Pro Leu Pro Pro Lys Lys Glu Asn Asp Glu Met Pro Thr Cys Leu Leu
          85          90          95
Cys Val Cys Leu Ser Gly Ser Val Tyr Cys Glu Glu Val Asp Ile Asp
          100          105          110
Ala Val Pro Pro Leu Pro Lys Glu Ser Ala Tyr Leu Tyr Ala Arg Phe
          115          120          125
Asn Lys Ile Lys Lys Leu Thr Ala Lys Asp Phe Ala Asp Ile Pro Asn
          130          135          140
Leu Arg Arg Leu Asp Phe Thr Gly Asn Leu Ile Glu Asp Ile Glu Asp
          145          150          155          160
Gly Thr Phe Ser Lys Leu Ser Leu Leu Glu Glu Leu Ser Leu Ala Glu
          165          170          175
Asn Gln Leu Leu Lys Leu Pro Val Leu Pro Pro Lys Leu Thr Leu Phe
          180          185          190
Asn Ala Lys Tyr Asn Lys Ile Lys Ser Arg Gly Ile Lys Ala Asn Ala
          195          200          205
Phe Lys Lys Leu Asn Asn Leu Thr Phe Leu Tyr Leu Asp His Asn Ala
          210          215          220
Leu Glu Ser Val Pro Leu Asn Leu Pro Glu Ser Leu Arg Val Ile His
          225          230          235          240
Leu Gln Phe Asn Asn Ile Ala Ser Ile Thr Asp Asp Thr Phe Cys Lys
          245          250          255
Ala Asn Asp Thr Ser Tyr Ile Arg Asp Arg Ile Glu Glu Ile Arg Leu
          260          265          270
Glu Gly Asn Pro Ile Val Leu Gly Lys His Pro Asn Ser Phe Ile Cys
          275          280          285
Leu Lys Arg Leu Pro Ile Gly Ser Tyr Phe
          290          295

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<210> 88

<211> 263

<212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (27)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (112)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 88
 Met Cys Leu Leu Gly Gly Leu Ser Ala Pro Pro Leu Leu Leu Leu Pro
 1 5 10 15
 Leu Leu Pro Leu Leu Leu Cys Pro Pro Thr Xaa Gln Gly Asp Cys Ser
 20 25 30
 Phe Pro Pro Glu Leu Pro Asn Ala Ile Gln Ser Val Gly Asp Gln Gln
 35 40 45
 Ser Phe Pro Glu Lys Phe Thr Val Thr Tyr Lys Cys Lys Glu Gly Phe
 50 55 60
 Val Lys Val Pro Gly Lys Ala Asp Ser Val Val Cys Leu Asn Asn Lys
 65 70 75 80
 Trp Ser Glu Val Ala Glu Phe Cys Asn Arg Ser Cys Asp Val Pro Thr
 85 90 95
 Arg Leu Gln Phe Ala Ser Leu Lys Lys Ser Phe Thr Lys Gln Asn Xaa
 100 105 110
 Phe Pro Val Gly Ser Val Val Glu Tyr Glu Cys Arg Pro Gly Tyr Gln
 115 120 125
 Arg Asp His Leu Leu Ser Gly Lys Leu Thr Cys Leu Leu Asn Phe Thr
 130 135 140
 Trp Ser Lys Pro Asp Glu Phe Cys Lys Arg Lys Ser Cys Pro Asn Pro
 145 150 155 160
 Gly Asp Leu Arg His Gly His Val Asn Ile Pro Thr Asp Ile Leu Tyr
 165 170 175
 Ala Ala Val Ile His Phe Ser Cys Asn Lys Gly Tyr Arg Leu Val Gly
 180 185 190
 Ala Ala Ser Ser Tyr Cys Ser Ile Val Asn Asp Asp Val Gly Trp Ser
 195 200 205
 Asp Pro Leu Pro Glu Cys Gln Glu Ile Phe Cys Pro Glu Pro Pro Lys
 210 215 220
 Ile Ser Asn Gly Val Ile Leu Asp Gln Gln Asn Thr Tyr Val Tyr Gln
 225 230 235 240
 Gln Ala Val Lys Tyr Glu Cys Ile Lys Gly Phe Thr Leu Ile Gly Glu
 245 250 255
 Asn Ser Asp Leu Leu Tyr Cys
 260

<210> 89
 <211> 1745
 <212> PRT
 <213> Homo sapiens

<400> 89

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Met Glu Cys Cys Arg Arg Ala Thr Pro Gly Thr Leu Leu Leu Phe Leu
 1          5          10          15

Ala Phe Leu Leu Leu Ser Ser Arg Thr Ala Arg Ser Glu Glu Asp Arg
          20          25          30

Asp Gly Leu Trp Asp Ala Trp Gly Pro Trp Ser Glu Cys Ser Arg Thr
          35          40          45

Cys Gly Gly Gly Ala Ser Tyr Ser Leu Arg Arg Cys Leu Ser Ser Lys
          50          55          60

Ser Cys Glu Gly Arg Asn Ile Arg Tyr Arg Thr Cys Ser Asn Val Asp
          65          70          75          80

Cys Pro Pro Glu Ala Gly Asp Phe Arg Ala Gln Gln Cys Ser Ala His
          85          90          95

Asn Asp Val Lys His His Gly Gln Phe Tyr Glu Trp Leu Pro Val Ser
          100          105          110

Asn Asp Pro Asp Asn Pro Cys Ser Leu Lys Cys Gln Ala Lys Gly Thr
          115          120          125

Thr Leu Val Val Glu Leu Ala Pro Lys Val Leu Asp Gly Thr Arg Cys
          130          135          140

Tyr Thr Glu Ser Leu Asp Met Cys Ile Ser Gly Leu Cys Gln Ile Val
          145          150          155          160

Gly Cys Asp His Gln Leu Gly Ser Thr Val Lys Glu Asp Asn Cys Gly
          165          170          175

Val Cys Asn Gly Asp Gly Ser Thr Cys Arg Leu Val Arg Gly Gln Tyr
          180          185          190

Lys Ser Gln Leu Ser Ala Thr Lys Ser Asp Asp Thr Val Val Ala Ile
          195          200          205

Pro Tyr Gly Ser Arg His Ile Arg Leu Val Leu Lys Gly Pro Asp His
          210          215          220

Leu Tyr Leu Glu Thr Lys Thr Leu Gln Gly Thr Lys Gly Glu Asn Ser
          225          230          235          240

Leu Ser Ser Thr Gly Thr Phe Leu Val Asp Asn Ser Ser Val Asp Phe
          245          250          255

Gln Lys Phe Pro Asp Lys Glu Ile Leu Arg Met Ala Gly Pro Leu Thr
          260          265          270

Ala Asp Phe Ile Val Lys Ile Arg Asn Ser Gly Ser Ala Asp Ser Thr
          275          280          285

Val Gln Phe Ile Phe Tyr Gln Pro Ile Ile His Arg Trp Arg Glu Thr
          290          295          300

Asp Phe Phe Pro Cys Ser Ala Thr Cys Gly Gly Gly Tyr Gln Leu Thr
          305          310          315          320

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Ser Ala Glu Cys Tyr Asp Leu Arg Ser Asn Arg Val Val Ala Asp Gln
 325 330 335
 Tyr Cys His Tyr Tyr Pro Glu Asn Ile Lys Pro Lys Pro Lys Leu Gln
 340 345 350
 Glu Cys Asn Leu Asp Pro Cys Pro Ala Arg Trp Glu Ala Thr Pro Trp
 355 360 365
 Thr Ala Cys Ser Ser Ser Cys Gly Gly Gly Ile Gln Ser Arg Ala Val
 370 375 380
 Ser Cys Val Glu Glu Asp Ile Gln Gly His Val Thr Ser Val Glu Glu
 385 390 395 400
 Trp Lys Cys Met Tyr Thr Pro Lys Met Pro Ile Ala Gln Pro Cys Asn
 405 410 415
 Ile Phe Asp Cys Pro Lys Trp Leu Ala Gln Glu Trp Ser Pro Cys Thr
 420 425 430
 Val Thr Cys Gly Gln Gly Leu Arg Tyr Arg Val Val Leu Cys Ile Asp
 435 440 445
 His Arg Gly Met His Thr Gly Gly Cys Ser Pro Lys Thr Lys Pro His
 450 455 460
 Ile Lys Glu Glu Cys Ile Val Pro Thr Pro Cys Tyr Lys Pro Lys Glu
 465 470 475 480
 Lys Leu Pro Val Glu Ala Lys Leu Pro Trp Phe Lys Gln Ala Gln Glu
 485 490 495
 Leu Glu Glu Gly Ala Ala Val Ser Glu Glu Pro Ser Phe Ile Pro Lys
 500 505 510
 Ala Trp Ser Ala Cys Thr Val Thr Cys Gly Val Gly Thr Gln Val Arg
 515 520 525
 Ile Val Arg Cys Gln Val Leu Leu Ser Phe Ser Gln Ser Val Ala Asp
 530 535 540
 Leu Pro Ile Asp Glu Cys Glu Gly Pro Lys Pro Ala Ser Gln Arg Ala
 545 550 555 560
 Cys Tyr Ala Gly Pro Cys Ser Gly Glu Ile Pro Glu Phe Asn Pro Asp
 565 570 575
 Glu Thr Asp Gly Leu Phe Gly Gly Leu Gln Asp Phe Asp Glu Leu Tyr
 580 585 590
 Asp Trp Glu Tyr Glu Gly Phe Thr Lys Cys Ser Glu Ser Cys Gly Gly
 595 600 605
 Gly Val Gln Glu Ala Val Val Ser Cys Leu Asn Lys Gln Thr Arg Glu
 610 615 620
 Pro Ala Glu Glu Asn Leu Cys Val Thr Ser Arg Arg Pro Pro Gln Leu
 625 630 635 640
 Leu Lys Ser Cys Asn Leu Asp Pro Cys Pro Ala Arg Trp Glu Ile Gly
 645 650 655
 Lys Trp Ser Pro Cys Ser Leu Thr Cys Gly Val Gly Leu Gln Thr Arg
 660 665 670

Asp Val Phe Cys Ser His Leu Leu Ser Arg Glu Met Asn Glu Thr Val
 675 680 685
 Ile Leu Ala Asp Glu Leu Cys Arg Gln Pro Lys Pro Ser Thr Val Gln
 690 695 700
 Ala Cys Asn Arg Phe Asn Cys Pro Pro Ala Trp Tyr Pro Ala Gln Trp
 705 710 715 720
 Gln Pro Cys Ser Arg Thr Cys Gly Gly Gly Val Gln Lys Arg Glu Val
 725 730 735
 Leu Cys Lys Gln Arg Met Ala Asp Gly Ser Phe Leu Glu Leu Pro Glu
 740 745 750
 Thr Phe Cys Ser Ala Ser Lys Pro Ala Cys Gln Gln Ala Cys Lys Lys
 755 760 765
 Asp Asp Cys Pro Ser Glu Trp Leu Leu Ser Asp Trp Thr Glu Cys Ser
 770 775 780
 Thr Ser Cys Gly Glu Gly Thr Gln Thr Arg Ser Ala Ile Cys Arg Lys
 785 790 795 800
 Met Leu Lys Thr Gly Leu Ser Thr Val Val Asn Ser Thr Leu Cys Pro
 805 810 815
 Pro Leu Pro Phe Ser Ser Ser Ile Arg Pro Cys Met Leu Ala Thr Cys
 820 825 830
 Ala Arg Pro Gly Arg Pro Ser Thr Lys His Ser Pro His Ile Ala Ala
 835 840 845
 Ala Arg Lys Val Tyr Ile Gln Thr Arg Arg Gln Arg Lys Leu His Phe
 850 855 860
 Val Val Gly Gly Phe Ala Tyr Leu Leu Pro Lys Thr Ala Val Val Leu
 865 870 875 880
 Arg Cys Pro Ala Arg Arg Val Arg Lys Pro Leu Ile Thr Trp Glu Lys
 885 890 895
 Asp Gly Gln His Leu Ile Ser Ser Thr His Val Thr Val Ala Pro Phe
 900 905 910
 Gly Tyr Leu Lys Ile His Arg Leu Lys Pro Ser Asp Ala Gly Val Tyr
 915 920 925
 Thr Cys Ser Ala Gly Pro Ala Arg Glu His Phe Val Ile Lys Leu Ile
 930 935 940
 Gly Gly Asn Arg Lys Leu Val Ala Arg Pro Leu Ser Pro Arg Ser Glu
 945 950 955 960
 Glu Glu Val Leu Ala Gly Arg Lys Gly Gly Pro Lys Glu Ala Leu Gln
 965 970 975
 Thr His Lys His Gln Asn Gly Ile Phe Ser Asn Gly Ser Lys Ala Glu
 980 985 990
 Lys Arg Gly Leu Ala Ala Asn Pro Gly Ser Arg Tyr Asp Asp Leu Val
 995 1000 1005
 Ser Arg Leu Leu Glu Gln Gly Gly Trp Pro Gly Glu Leu Leu Ala Ser
 1010 1015 1020

Trp Glu Ala Gln Asp Ser Ala Glu Arg Asn Thr Thr Ser Glu Glu Asp
 1030 1035 1040
 Pro Gly Ala Glu Gln Val Leu Leu His Leu Pro Phe Thr Met Val Thr
 1045 1050 1055
 Glu Gln Arg Arg Leu Asp Asp Ile Leu Gly Asn Leu Ser Gln Gln Pro
 1060 1065 1070
 Glu Glu Leu Arg Asp Leu Tyr Ser Lys His Leu Val Ala Gln Leu Ala
 1075 1080 1085
 Gln Glu Ile Phe Arg Ser His Leu Glu His Gln Asp Thr Leu Leu Lys
 1090 1095 1100
 Pro Ser Glu Arg Arg Thr Ser Pro Val Thr Leu Ser Pro His Lys His
 1110 1115 1120
 Val Ser Gly Phe Ser Ser Ser Leu Arg Thr Ser Ser Thr Gly Asp Ala
 1125 1130 1135
 Gly Gly Gly Ser Arg Arg Pro His Arg Lys Pro Thr Ile Leu Arg Lys
 1140 1145 1150
 Ile Ser Ala Ala Gln Gln Leu Ser Ala Ser Glu Val Val Thr His Leu
 1155 1160 1165
 Gly Gln Thr Val Ala Leu Ala Ser Gly Thr Leu Ser Val Leu Leu His
 1170 1175 1180
 Cys Glu Ala Ile Gly His Pro Arg Pro Thr Ile Ser Trp Ala Arg Asn
 1190 1195 1200
 Gly Glu Glu Val Gln Phe Ser Asp Arg Ile Leu Leu Gln Pro Asp Asp
 1205 1210 1215
 Ser Leu Gln Ile Leu Ala Pro Val Glu Ala Asp Val Gly Phe Tyr Thr
 1220 1225 1230
 Cys Asn Ala Thr Asn Ala Leu Gly Tyr Asp Ser Val Ser Ile Ala Val
 1235 1240 1245
 Thr Leu Ala Gly Lys Pro Leu Val Lys Thr Ser Arg Met Thr Val Ile
 1250 1255 1260
 Asn Thr Glu Lys Pro Ala Val Thr Val Asp Ile Gly Ser Thr Ile Lys
 1270 1275 1280
 Thr Val Gln Gly Val Asn Val Thr Ile Asn Cys Gln Val Ala Gly Val
 1285 1290 1295
 Pro Glu Ala Glu Val Thr Trp Phe Arg Asn Lys Ser Lys Leu Gly Ser
 1300 1305 1310
 Pro His His Leu His Glu Gly Ser Leu Leu Leu Thr Asn Val Ser Ser
 1315 1320 1325
 Ser Asp Gln Gly Leu Tyr Ser Cys Arg Ala Ala Asn Leu His Gly Glu
 1330 1335 1340
 Leu Thr Glu Ser Thr Gln Leu Leu Ile Leu Asp Pro Pro Gln Val Pro
 1350 1355 1360
 Thr Gln Leu Glu Asp Ile Arg Ala Leu Leu Ala Ala Thr Gly Pro Asn
 1365 1370 1375

Leu Pro Ser Val Leu Thr Ser Pro Leu Gly Thr Gln Leu Val Leu Asp
 1380 1385 1390
 Pro Gly Asn Ser Ala Leu Leu Gly Cys Pro Ile Lys Gly His Pro Val
 1395 1400 1405
 Pro Asn Ile Thr Trp Phe His Gly Gly Gln Pro Ile Val Thr Ala Thr
 1410 1415 1420
 Gly Leu Thr His His Ile Leu Ala Ala Gly Gln Ile Leu Gln Val Ala
 1430 1435 1440
 Asn Leu Ser Gly Gly Ser Gln Gly Glu Phe Ser Cys Leu Ala Gln Asn
 1445 1450 1455
 Glu Ala Gly Val Leu Met Gln Lys Ala Ser Leu Val Ile Gln Asp Tyr
 1460 1465 1470
 Trp Trp Ser Val Asp Arg Leu Ala Thr Cys Ser Ala Ser Cys Gly Asn
 1475 1480 1485
 Arg Gly Val Gln Gln Pro Arg Leu Arg Cys Leu Leu Asn Ser Thr Glu
 1490 1495 1500
 Val Asn Pro Ala His Cys Ala Gly Lys Val Arg Pro Ala Val Gln Pro
 1510 1515 1520
 Ile Ala Cys Asn Arg Arg Asp Cys Pro Ser Arg Trp Met Val Thr Ser
 1525 1530 1535
 Trp Ser Ala Cys Thr Arg Ser Cys Gly Gly Gly Val Gln Thr Arg Arg
 1540 1545 1550
 Val Thr Cys Gln Lys Leu Lys Ala Ser Gly Ile Ser Thr Pro Val Ser
 1555 1560 1565
 Asn Asp Met Cys Thr Gln Val Ala Lys Arg Pro Val Asp Thr Gln Ala
 1570 1575 1580
 Cys Asn Gln Gln Leu Cys Val Glu Trp Ala Phe Ser Ser Trp Gly Gln
 1590 1595 1600
 Cys Asn Gly Pro Cys Ile Gly Pro His Leu Ala Val Gln His Arg Gln
 1605 1610 1615
 Val Phe Cys Gln Thr Arg Asp Gly Ile Thr Leu Pro Ser Glu Gln Cys
 1620 1625 1630
 Ser Ala Leu Pro Arg Pro Val Ser Thr Gln Asn Cys Trp Ser Glu Ala
 1635 1640 1645
 Cys Ser Val His Trp Arg Val Ser Leu Trp Thr Leu Cys Thr Ala Thr
 1650 1655 1660
 Cys Gly Asn Tyr Gly Phe Gln Ser Arg Arg Val Glu Cys Val His Ala
 1670 1675 1680
 Arg Thr Asn Lys Ala Val Pro Glu His Leu Cys Ser Trp Gly Pro Arg
 1685 1690 1695
 Pro Ala Asn Trp Gln Arg Cys Asn Ile Thr Pro Cys Glu Asn Met Glu
 1700 1705 1710
 Cys Arg Asp Thr Thr Arg Tyr Cys Glu Lys Val Lys Gln Leu Lys Leu
 1715 1720 1725

Cys Gln Leu Ser Gln Phe Lys Ser Arg Cys Cys Gly Thr Cys Gly Lys
 1730 1735 1740

Ala

<210> 90
 <211> 142
 <212> PRT
 <213> Homo sapiens

<400> 90
 Met Arg Arg Leu Leu Leu Val Thr Ser Leu Val Val Val Leu Leu Trp
 1 5 10 15
 Glu Ala Gly Ala Val Pro Ala Pro Lys Val Pro Ile Lys Met Gln Val
 20 25 30
 Lys His Trp Pro Ser Glu Gln Asp Pro Glu Lys Ala Trp Gly Ala Arg
 35 40 45
 Val Val Glu Pro Pro Glu Lys Asp Asp Gln Leu Val Val Leu Phe Pro
 50 55 60
 Val Gln Lys Pro Lys Leu Leu Thr Thr Glu Glu Lys Pro Arg Gly Thr
 65 70 75 80
 Lys Ala Trp Met Glu Thr Glu Asp Thr Leu Gly Arg Val Leu Ser Pro
 85 90 95
 Glu Pro Asp His Asp Ser Leu Tyr His Pro Pro Pro Glu Glu Asp Gln
 100 105 110
 Gly Glu Glu Arg Pro Arg Leu Trp Val Met Pro Asn His Gln Val Leu
 115 120 125
 Leu Gly Pro Glu Glu Asp Gln Asp His Ile Tyr His Pro Gln
 130 135 140

<210> 91
 <211> 350
 <212> PRT
 <213> Homo sapiens

<400> 91
 Met Ala Val Phe Val Val Leu Leu Ala Leu Val Ala Gly Val Leu Gly
 1 5 10 15
 Asn Glu Phe Ser Ile Leu Lys Ser Pro Gly Ser Val Val Phe Arg Asn
 20 25 30
 Gly Asn Trp Pro Ile Pro Gly Glu Arg Ile Pro Asp Val Ala Ala Leu
 35 40 45
 Ser Met Gly Phe Ser Val Lys Glu Asp Leu Ser Trp Pro Gly Leu Ala
 50 55 60
 Val Gly Asn Leu Phe His Arg Pro Arg Ala Thr Val Met Val Met Val
 65 70 75 80
 Lys Gly Val Asn Lys Leu Ala Leu Pro Pro Gly Ser Val Ile Ser Tyr
 85 90 95
 Pro Leu Glu Asn Ala Val Pro Phe Ser Leu Asp Ser Val Ala Asn Ser

60

100					105					110					
Ile	His	Ser	Leu	Phe	Ser	Glu	Glu	Thr	Pro	Val	Val	Leu	Gln	Leu	Ala
		115					120					125			
Pro	Ser	Glu	Glu	Arg	Val	Tyr	Met	Val	Gly	Lys	Ala	Asn	Ser	Val	Phe
		130				135					140				
Glu	Asp	Leu	Ser	Val	Thr	Leu	Arg	Gln	Leu	Arg	Asn	Arg	Leu	Phe	Gln
	145					150					155				160
Glu	Asn	Ser	Val	Leu	Ser	Ser	Leu	Pro	Leu	Asn	Ser	Leu	Ser	Arg	Asn
			165					170						175	
Asn	Glu	Val	Asp	Leu	Leu	Phe	Leu	Ser	Glu	Leu	Gln	Val	Leu	His	Asp
			180					185						190	
Ile	Ser	Ser	Leu	Leu	Ser	Arg	His	Lys	His	Leu	Ala	Lys	Asp	His	Ser
		195					200					205			
Pro	Asp	Leu	Tyr	Ser	Leu	Glu	Leu	Ala	Gly	Leu	Asp	Glu	Ile	Gly	Lys
	210					215					220				
Arg	Tyr	Gly	Glu	Asp	Ser	Glu	Gln	Phe	Arg	Asp	Ala	Ser	Lys	Ile	Leu
	225					230					235				240
Val	Asp	Ala	Leu	Gln	Lys	Phe	Ala	Asp	Asp	Met	Tyr	Ser	Leu	Tyr	Gly
			245					250						255	
Gly	Asn	Ala	Val	Val	Glu	Leu	Val	Thr	Val	Lys	Ser	Phe	Asp	Thr	Ser
			260					265					270		
Leu	Ile	Arg	Lys	Thr	Arg	Thr	Ile	Leu	Glu	Ala	Lys	Gln	Ala	Lys	Asn
		275					280					285			
Pro	Ala	Ser	Pro	Tyr	Asn	Leu	Ala	Tyr	Lys	Tyr	Asn	Phe	Glu	Tyr	Ser
	290					295					300				
Val	Val	Phe	Asn	Met	Val	Leu	Trp	Ile	Met	Ile	Ala	Leu	Ala	Leu	Ala
	305					310					315				320
Val	Ile	Ile	Thr	Ser	Tyr	Asn	Ile	Trp	Asn	Met	Asp	Pro	Gly	Tyr	Asp
			325					330					335		
Ser	Ile	Ile	Tyr	Arg	Met	Thr	Asn	Gln	Lys	Ile	Arg	Met	Asp		
			340					345					350		

<210> 92

<211> 102

<212> PRT

<213> Homo sapiens

<400> 92

Met	Lys	Pro	Ala	Thr	Ala	Ser	Ala	Leu	Leu	Leu	Leu	Leu	Leu	Gly	Leu
1				5					10					15	
Ala	Trp	Thr	Gln	Gly	Ser	His	Gly	Trp	Gly	Ala	Asp	Ala	Ser	Ser	Leu
			20					25					30		
Gln	Lys	Arg	Ala	Gly	Arg	Ala	Asp	Gln	Pro	Gly	Ala	Gly	Trp	Gln	Glu
		35					40					45			
Val	Ala	Ala	Val	Thr	Ser	Lys	Asn	Tyr	Asn	Tyr	Asn	Gln	His	Ala	Tyr
	50					55					60				

Pro Thr Ala Tyr Gly Gly Lys Tyr Ser Val Lys Thr Pro Ala Lys Gly
 65 70 75 80
 Gly Val Ser Pro Ser Ser Ser Ala Ser Arg Val Gln Pro Gly Leu Leu
 85 90 95
 Gln Trp Val Lys Phe Trp
 100

<210> 93
 <211> 509
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (20)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (168)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (199)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (244)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (246)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (294)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (301)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
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 <222> (303)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (493)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE
 <222> (498)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (499)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (505)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 93
 Met Glu Glu Leu Ala Thr Glu Lys Glu Ala Glu Glu Ser His Arg Gln
 1 5 10 15
 Asp Ser Val Xaa Leu Leu Thr Phe Ile Leu Leu Leu Thr Leu Thr Ile
 20 25 30
 Leu Thr Ile Trp Leu Phe Lys His Arg Arg Val Arg Phe Leu His Glu
 35 40 45
 Thr Gly Leu Ala Met Ile Tyr Gly Leu Ile Val Gly Val Ile Leu Arg
 50 55 60
 Tyr Gly Thr Pro Ala Thr Ser Gly Arg Asp Lys Ser Leu Ser Cys Thr
 65 70 75 80
 Gln Glu Asp Arg Ala Phe Ser Thr Leu Leu Val Asn Val Ser Gly Lys
 85 90 95
 Phe Phe Glu Tyr Thr Leu Lys Gly Glu Ile Ser Pro Gly Lys Ile Asn
 100 105 110
 Ser Val Glu Gln Asn Asp Met Leu Arg Lys Val Thr Phe Asp Pro Glu
 115 120 125
 Val Phe Phe Asn Ile Leu Leu Pro Pro Ile Ile Phe His Ala Gly Tyr
 130 135 140
 Ser Leu Lys Lys Arg His Phe Phe Arg Asn Leu Gly Ser Ile Leu Ala
 145 150 155 160
 Tyr Ala Phe Leu Gly Thr Ala Xaa Ser Cys Phe Ile Ile Gly Asn Leu
 165 170 175
 Met Tyr Gly Val Val Lys Leu Met Lys Ile Met Gly Gln Leu Ser Asp
 180 185 190
 Lys Phe Tyr Tyr Thr Xaa Xaa Leu Phe Phe Gly Ala Ile Ile Ser Ala
 195 200 205
 Thr Asp Pro Val Thr Val Leu Ala Ile Phe Asn Glu Leu His Ala Asp
 210 215 220
 Val Asp Leu Tyr Ala Leu Leu Phe Gly Glu Ser Val Leu Asn Asp Ala
 225 230 235 240
 Val Ala Ile Xaa Leu Xaa Ser Ser Ile Val Ala Tyr Gln Pro Ala Gly
 245 250 255
 Leu Asn Thr His Ala Phe Asp Ala Ala Ala Phe Phe Lys Ser Val Gly
 260 265 270

Ile Phe Leu Gly Ile Phe Ser Gly Ser Phe Thr Met Gly Ala Val Thr
 275 280 285
 Gly Val Val Thr Ala Xaa Val Thr Lys Phe Thr Lys Xaa His Xaa Phe
 290 295 300
 Pro Leu Leu Glu Thr Ala Leu Phe Phe Leu Met Ser Trp Ser Thr Phe
 305 310 315 320
 Leu Leu Ala Glu Ala Cys Gly Phe Thr Gly Val Val Ala Val Leu Phe
 325 330 335
 Cys Gly Ile Thr Gln Ala His Tyr Thr Tyr Asn Asn Leu Ser Val Glu
 340 345 350
 Ser Arg Ser Arg Thr Lys Gln Leu Phe Glu Val Leu His Phe Leu Ala
 355 360 365
 Glu Asn Phe Ile Phe Ser Tyr Met Gly Leu Ala Leu Phe Thr Phe Gln
 370 375 380
 Lys His Val Phe Ser Pro Ile Phe Ile Ile Gly Ala Phe Val Ala Ile
 385 390 395 400
 Phe Leu Gly Arg Ala Ala His Ile Tyr Pro Leu Ser Phe Phe Leu Asn
 405 410 415
 Leu Gly Arg Arg His Lys Ile Gly Trp Asn Phe Gln His Met Met Met
 420 425 430
 Phe Ser Gly Leu Arg Gly Ala Met Ala Phe Ala Leu Ala Ile Arg Asp
 435 440 445
 Thr Ala Ser Tyr Ala Arg Gln Met Met Phe Thr Thr Thr Leu Leu Ile
 450 455 460
 Val Phe Phe Thr Val Trp Ile Ile Gly Gly Gly Thr Thr Pro Met Leu
 465 470 475 480
 Ser Trp Leu Asn Ile Arg Val Gly Val Asp Pro Asp Xaa Asp Pro Pro
 485 490 495
 Pro Xaa Xaa Asp Ser Phe Ala Phe Xaa Thr Glu Thr Ala
 500 505

<210> 94
 <211> 146
 <212> PRT
 <213> Homo sapiens

<400> 94
 Met Thr Met Arg Ser Leu Leu Arg Thr Pro Phe Leu Cys Gly Leu Leu
 1 5 10 15
 Trp Ala Phe Cys Ala Pro Gly Ala Arg Ala Glu Glu Pro Ala Ala Ser
 20 25 30
 Phe Ser Gln Pro Gly Ser Met Gly Leu Asp Lys Asn Thr Val His Asp
 35 40 45
 Gln Glu His Ile Met Glu His Leu Glu Gly Val Ile Asn Lys Pro Glu
 50 55 60
 Ala Glu Met Ser Pro Gln Glu Leu Gln Leu His Tyr Phe Lys Met His
 65 70 75 80

Asp Tyr Asp Gly Asn Asn Leu Leu Asp Gly Leu Glu Leu Ser Thr Ala
 85 90 95

Ile Thr His Val His Lys Glu Glu Gly Ser Glu Gln Ala Pro Leu Met
 100 105 110

Ser Glu Asp Glu Leu Ile Asn Ile Ile Asp Gly Val Leu Arg Asp Asp
 115 120 125

Asp Lys Asn Asn Asp Gly Tyr Ile Asp Tyr Ala Glu Phe Ala Lys Ser
 130 135 140

Leu Gln
 145

<210> 95
 <211> 626
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (353)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (354)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (363)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 95
 Met Gln Arg Ala Asp Ser Glu Gln Pro Ser Lys Arg Pro Arg Cys Asp
 1 5 10 15

Asp Ser Pro Arg Thr Pro Ser Asn Thr Pro Ser Ala Glu Ala Asp Trp
 20 25 30

Ser Pro Gly Leu Glu Leu His Pro Asp Tyr Lys Thr Trp Gly Pro Glu
 35 40 45

Gln Val Cys Ser Phe Leu Arg Arg Gly Gly Phe Glu Glu Pro Val Leu
 50 55 60

Leu Lys Asn Ile Arg Glu Asn Glu Ile Thr Gly Ala Leu Leu Pro Cys
 65 70 75 80

Leu Asp Glu Ser Arg Phe Glu Asn Leu Gly Val Ser Ser Leu Gly Glu
 85 90 95

Arg Lys Lys Leu Leu Ser Tyr Ile Gln Arg Leu Val Gln Ile His Val
 100 105 110

Asp Thr Met Lys Val Ile Asn Asp Pro Ile His Gly His Ile Glu Leu
 115 120 125

His Pro Leu Leu Val Arg Ile Ile Asp Thr Pro Gln Phe Gln Arg Leu
 130 135 140

Arg Tyr Ile Lys Gln Leu Gly Gly Gly Tyr Tyr Val Phe Pro Gly Ala

65

145		150		155		160
Ser His Asn Arg	Phe Glu His Ser Leu Gly Val Gly Tyr Leu Ala Gly					
	165			170		175
Cys Leu Val His	Ala Leu Gly Glu Lys Gln Pro Glu Leu Gln Ile Ser					
	180		185			190
Glu Arg Asp Val	Leu Cys Val Gln Ile Ala Gly Leu Cys His Asp Leu					
	195		200			205
Gly His Gly Pro	Phe Ser His Met Phe Asp Gly Arg Phe Ile Pro Leu					
	210		215			220
Ala Arg Pro Glu	Val Lys Trp Thr His Glu Gln Gly Ser Val Met Met					
	225		230			235
Phe Glu His Leu	Ile Asn Ser Asn Gly Ile Lys Pro Val Met Glu Gln					
	245		250			255
Tyr Gly Leu Ile	Pro Glu Glu Asp Ile Cys Phe Ile Lys Glu Gln Ile					
	260		265			270
Val Gly Pro Leu	Glu Ser Pro Val Glu Asp Ser Leu Trp Pro Tyr Lys					
	275		280			285
Gly Arg Pro Glu	Asn Lys Ser Phe Leu Tyr Glu Ile Val Ser Asn Lys					
	290		295			300
Arg Asn Gly Ile	Asp Val Asp Lys Trp Asp Tyr Phe Ala Arg Asp Cys					
	305		310			315
His His Leu Gly	Ile Gln Asn Asn Phe Asp Tyr Lys Arg Phe Ile Lys					
	325		330			335
Phe Ala Arg Val	Cys Glu Val Asp Asn Glu Leu Arg Ile Cys Ala Arg					
	340		345			350
Xaa Xaa Glu Val	Gly Asn Leu Tyr Asp Met Xaa His Thr Arg Asn Ser					
	355		360			365
Leu His Arg Arg	Ala Tyr Gln His Lys Val Gly Asn Ile Ile Asp Thr					
	370		375			380
Met Ile Thr Asp	Ala Phe Leu Lys Ala Asp Asp Tyr Ile Glu Ile Thr					
	385		390			395
Gly Ala Gly Gly	Lys Lys Tyr Arg Ile Ser Thr Ala Ile Asp Asp Met					
	405		410			415
Glu Ala Tyr Thr	Lys Leu Thr Asp Asn Ile Phe Leu Glu Ile Leu Tyr					
	420		425			430
Ser Thr Asp Pro	Lys Leu Lys Asp Ala Arg Glu Ile Leu Lys Gln Ile					
	435		440			445
Glu Tyr Arg Asn	Leu Phe Lys Tyr Val Gly Glu Thr Gln Pro Thr Gly					
	450		455			460
Gln Ile Lys Ile	Lys Arg Glu Asp Tyr Glu Ser Leu Pro Lys Glu Val					
	465		470			475
Ala Ser Ala Lys	Pro Lys Val Leu Leu Asp Val Lys Leu Lys Ala Glu					
	485		490			495
Asp Phe Ile Val	Asp Val Ile Asn Met Asp Tyr Gly Met Gln Glu Lys					

500					505					510					
Asn	Pro	Ile	Asp	His	Val	Ser	Phe	Tyr	Cys	Lys	Thr	Ala	Pro	Asn	Arg
		515					520					525			
Ala	Ile	Arg	Ile	Thr	Lys	Asn	Gln	Val	Ser	Gln	Leu	Leu	Pro	Glu	Lys
	530					535					540				
Phe	Ala	Glu	Gln	Leu	Ile	Arg	Val	Tyr	Cys	Lys	Lys	Val	Asp	Arg	Lys
545					550					555					560
Ser	Leu	Tyr	Ala	Ala	Arg	Gln	Tyr	Phe	Val	Gln	Trp	Cys	Ala	Asp	Arg
				565					570					575	
Asn	Phe	Thr	Lys	Pro	Gln	Asp	Gly	Asp	Val	Ile	Ala	Pro	Leu	Ile	Thr
			580					585						590	
Pro	Gln	Lys	Lys	Glu	Trp	Asn	Asp	Ser	Thr	Ser	Val	Gln	Asn	Pro	Thr
		595					600					605			
Arg	Leu	Arg	Glu	Ala	Ser	Lys	Ser	Arg	Val	Gln	Leu	Phe	Lys	Asp	Asp
	610					615					620				
Pro	Met														
625															

<210> 96
 <211> 81
 <212> PRT
 <213> Homo sapiens

<400> 96
 Met Arg Leu Leu Val Leu Ser Ser Leu Leu Cys Ile Leu Leu Leu Cys
 1 5 10 15
 Phe Ser Ile Phe Ser Thr Glu Gly Lys Arg Arg Pro Ala Lys Ala Trp
 20 25 30
 Ser Gly Arg Arg Thr Arg Leu Cys Cys His Arg Val Pro Ser Pro Asn
 35 40 45
 Ser Thr Asn Leu Lys Gly His His Val Arg Leu Cys Lys Pro Cys Lys
 50 55 60
 Leu Glu Pro Glu Pro Arg Leu Trp Val Val Pro Gly Ala Leu Pro Gln
 65 70 75 80
 Val

<210> 97
 <211> 86
 <212> PRT
 <213> Homo sapiens

<400> 97
 Met Leu Trp Ala Leu Asp Ser Leu Leu Phe Phe Ser His Ala Gln Leu
 1 5 10 15
 Val Pro Leu Gly Gly Gly Glu Glu Trp Gly Ser Pro Gly Leu Gly Leu
 20 25 30
 His Ser Ile Ile Pro Ser Gln Ala Ser Gln Gly Val Ser Ala Pro Ala
 35 40 45

Gln Asp Leu Ala Gly Arg Ala Pro Tyr Arg Glu Ser Leu Gly Arg Leu
 50 55 60
 Ser Arg Leu Met Ala Gly Pro Ala Arg Gly Val Leu Arg Pro Ala Leu
 65 70 75 80
 Arg Thr Cys Pro Leu Phe
 85

<210> 98
 <211> 613
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (507)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 98
 Met Gly Ala Leu Arg Pro Thr Leu Leu Pro Pro Ser Leu Pro Leu Leu
 1 5 10 15
 Leu Leu Leu Met Leu Gly Met Gly Cys Trp Ala Arg Glu Val Leu Val
 20 25 30
 Pro Glu Gly Pro Leu Tyr Arg Val Ala Gly Thr Ala Val Ser Ile Ser
 35 40 45
 Cys Asn Val Thr Gly Tyr Glu Gly Pro Ala Gln Gln Asn Phe Glu Trp
 50 55 60
 Phe Leu Tyr Arg Pro Glu Ala Pro Asp Thr Ala Leu Gly Ile Val Ser
 65 70 75 80
 Thr Lys Asp Thr Gln Phe Ser Tyr Ala Val Phe Lys Ser Arg Val Val
 85 90 95
 Ala Gly Glu Val Gln Val Gln Arg Leu Gln Gly Asp Ala Val Val Leu
 100 105 110
 Lys Ile Ala Arg Leu Gln Ala Gln Asp Ala Gly Ile Tyr Glu Cys His
 115 120 125
 Thr Pro Ser Thr Asp Thr Arg Tyr Leu Gly Ser Tyr Ser Gly Lys Val
 130 135 140
 Glu Leu Arg Val Leu Pro Asp Val Leu Gln Val Ser Ala Ala Pro Pro
 145 150 155 160
 Gly Pro Arg Gly Arg Gln Ala Pro Thr Ser Pro Pro Arg Met Thr Val
 165 170 175
 His Glu Gly Gln Glu Leu Ala Leu Gly Cys Leu Ala Arg Thr Ser Thr
 180 185 190
 Gln Lys His Thr His Leu Ala Val Ser Phe Gly Arg Ser Val Pro Glu
 195 200 205
 Ala Pro Val Gly Arg Ser Thr Leu Gln Glu Val Val Gly Ile Arg Ser
 210 215 220
 Asp Leu Ala Val Glu Ala Gly Ala Pro Tyr Ala Glu Arg Leu Ala Ala
 225 230 235 240

Gly Glu Leu Arg Leu Gly Lys Glu Gly Thr Asp Arg Tyr Arg Met Val
 245 250 255
 Val Gly Gly Ala Gln Ala Gly Asp Ala Gly Thr Tyr His Cys Thr Ala
 260 265 270
 Ala Glu Trp Ile Gln Asp Pro Asp Gly Ser Trp Ala Gln Ile Ala Glu
 275 280 285
 Lys Arg Ala Val Leu Ala His Val Asp Val Gln Thr Leu Ser Ser Gln
 290 295 300
 Leu Ala Val Thr Val Gly Pro Gly Glu Arg Arg Ile Gly Pro Gly Glu
 305 310 315 320
 Pro Leu Glu Leu Leu Cys Asn Val Ser Gly Ala Leu Pro Pro Ala Gly
 325 330 335
 Arg His Ala Ala Tyr Ser Val Gly Trp Glu Met Ala Pro Ala Gly Ala
 340 345 350
 Pro Gly Pro Gly Arg Leu Val Ala Gln Leu Asp Thr Glu Gly Val Gly
 355 360 365
 Ser Leu Gly Pro Gly Tyr Glu Gly Arg His Ile Ala Met Glu Lys Val
 370 375 380
 Ala Ser Arg Thr Tyr Arg Leu Arg Leu Glu Ala Ala Arg Pro Gly Asp
 385 390 395 400
 Ala Gly Thr Tyr Arg Cys Leu Ala Lys Ala Tyr Val Arg Gly Ser Gly
 405 410 415
 Thr Arg Leu Arg Glu Ala Ala Ser Ala Arg Ser Arg Pro Leu Pro Val
 420 425 430
 His Val Arg Glu Glu Gly Val Val Leu Glu Ala Val Ala Trp Leu Ala
 435 440 445
 Gly Gly Thr Val Tyr Arg Gly Glu Thr Ala Ser Leu Leu Cys Asn Ile
 450 455 460
 Ser Val Arg Gly Gly Pro Pro Gly Leu Arg Leu Ala Ala Ser Trp Trp
 465 470 475 480
 Val Glu Arg Pro Glu Asp Gly Glu Leu Ser Ser Val Pro Ala Gln Leu
 485 490 495
 Val Gly Gly Val Gly Gln Asp Gly Val Ala Xaa Leu Gly Val Arg Pro
 500 505 510
 Gly Gly Gly Pro Val Ser Val Glu Leu Val Gly Pro Arg Ser His Arg
 515 520 525
 Leu Arg Leu His Ser Leu Gly Pro Glu Asp Glu Gly Val Tyr His Cys
 530 535 540
 Ala Pro Ser Ala Trp Val Gln His Ala Asp Tyr Ser Trp Tyr Gln Ala
 545 550 555 560
 Gly Ser Ala Arg Ser Gly Pro Val Thr Val Tyr Pro Tyr Met His Ala
 565 570 575
 Leu Asp Thr Leu Phe Val Pro Leu Leu Val Gly Thr Gly Val Ala Leu
 580 585 590

Val Thr Gly Ala Thr Val Leu Gly Thr Ile Thr Cys Cys Phe Met Lys
595 600 605

Arg Leu Arg Lys Arg
610

```
<210> 99
<211> 60
<212> PRT
<213> Homo sapiens
```

<400> 99
Met Ala Trp Ala Val Thr Leu Ile Leu Ser Leu Ser Arg Ala Val Arg
1 5 10 15

Thr Gln Glu Val Pro Met Ala Leu Gln Ala His Ser Gly Ile Gln Leu
20 25 30

Ala Ser Arg Val Gly Leu Pro Gly Pro Trp Pro Glu Cys Ser Thr Leu
35 40 45

Ser Ser Arg Cys His Leu Ser Met Asp Ser Lys Val
50 55 60

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<210> 100
<211> 167
<212> PRT
<213> Homo sapiens
```

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<220>
<221> SITE
<222> (61)
<223> Xaa equals any of the naturally occurring L-amino acids
```

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<220>
<221> SITE
<222> (79)
<223> Xaa equals any of the naturally occurring L-amino acids
```

<400> 100
Met Cys Ser Leu Phe His Ala Phe Ile Phe Ala Gln Leu Trp Thr Val
1 5 10 15

Tyr Cys Glu Gln Ser Ala Val Ala Thr Asn Leu Gln Asn Gln Asn Glu
20 25 30

Phe Ser Phe Thr Ala Ile Leu Thr Ala Leu Glu Phe Trp Ser Arg Val
35 40 45

Thr Pro Ser Ile Leu Gln Leu Met Ala His Asn Lys Xaa Met Val Glu
50 55 60

Met Val Cys Leu His Val Ile Ser Leu Met Glu Ala Leu Gln Xaa Cys
65 70 75 80

Asn Ser Thr Ile Phe Val Lys Leu Ile Pro Met Trp Leu Pro Met Ile
85 90 95

Gln Ser Asn Ile Lys His Leu Ser Ala Gly Leu Gln Leu Arg Leu Gln
100 105 110

Ala Ile Gln Asn His Val Asn His His Ser Leu Arg Thr Leu Pro Gly
115 120 125

Ser Gly Gln Ser Ser Ala Gly Leu Ala Ala Leu Arg Lys Trp Leu Gln
 130 135 140

Cys Thr Gln Phe Lys Met Ala Gln Val Glu Ile Gln Ser Ser Glu Ala
 145 150 155 160

Ala Ser Gln Phe Tyr Pro Leu
 165

<210> 101
 <211> 183
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (86)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (146)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 101
 Met Ala Val Gly Lys Phe Leu Leu Gly Ser Leu Leu Leu Leu Ser Leu
 1 5 10 15

Gln Leu Gly Gln Gly Trp Gly Pro Asp Ala Arg Gly Val Pro Val Ala
 20 25 30

Asp Gly Glu Phe Ser Ser Glu Gln Val Ala Lys Ala Gly Gly Thr Trp
 35 40 45

Leu Gly Lys Asp Phe Gln Gly Pro Ser Val Thr Ser Gln Leu Ser Pro
 50 55 60

Ala Leu Thr Leu Leu Thr Val Ser Ala Leu Pro Ser His Arg His Pro
 65 70 75 80

Pro Pro Pro Cys Pro Xaa Ala Pro Ser Pro Val Trp Ser Met Pro Ala
 85 90 95

Val Glu Pro Asp Pro Val Arg Gly Arg Ala Arg Pro Gly Leu Arg Leu
 100 105 110

Ile Gly Glu Val Ile Phe Arg Tyr Cys Ala Gly Ser Cys Pro Arg Gly
 115 120 125

Ala Arg Thr Gln His Gly Leu Ala Leu Ala Arg Leu Gln Gly Gln Gly
 130 135 140

Arg Xaa His Gly Gly Pro Cys Cys Arg Pro Thr Arg Tyr Thr Asp Val
 145 150 155 160

Ala Phe Leu Asp Asp Arg His Ala Gly Ser Gly Cys Pro Ser Ser Arg
 165 170 175

Arg Leu Cys Gly Cys Gly Gly
 180

<210> 102
 <211> 239

<212> PRT

<213> Homo sapiens

<400> 102

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Met Ala Tyr Gln Ser Leu Arg Leu Glu Tyr Leu Gln Ile Pro Pro Val
 1          5          10          15

Ser Arg Ala Tyr Thr Thr Ala Cys Val Leu Thr Thr Ala Ala Val Gln
          20          25          30

Leu Glu Leu Ile Thr Pro Phe Gln Leu Tyr Phe Asn Pro Glu Leu Ile
          35          40          45

Phe Lys His Phe Gln Ile Trp Arg Leu Ile Thr Asn Phe Leu Phe Phe
 50          55          60

Gly Pro Val Gly Phe Asn Phe Leu Phe Asn Met Ile Phe Leu Tyr Arg
65          70          75          80

Tyr Cys Arg Met Leu Glu Glu Gly Ser Phe Arg Gly Arg Thr Ala Asp
          85          90          95

Phe Val Phe Met Phe Leu Phe Gly Gly Phe Leu Met Thr Leu Phe Gly
          100          105          110

Leu Phe Val Ser Leu Val Phe Leu Gly Gln Ala Phe Thr Ile Met Leu
          115          120          125

Val Tyr Val Trp Ser Arg Arg Asn Pro Tyr Val Arg Met Asn Phe Phe
          130          135          140

Gly Leu Leu Asn Phe Gln Ala Pro Phe Leu Pro Trp Val Leu Met Gly
145          150          155          160

Phe Ser Leu Leu Leu Gly Asn Ser Ile Ile Val Asp Leu Leu Gly Ile
          165          170          175

Ala Val Gly His Ile Tyr Phe Phe Leu Glu Asp Val Phe Pro Asn Gln
          180          185          190

Pro Gly Gly Ile Arg Ile Leu Lys Thr Pro Ser Ile Leu Lys Ala Ile
          195          200          205

Phe Asp Thr Pro Asp Glu Asp Pro Asn Tyr Asn Pro Leu Pro Glu Glu
210          215          220

Arg Pro Gly Gly Phe Ala Trp Gly Glu Gly Gln Arg Leu Gly Gly
225          230          235

```

<210> 103

<211> 89

<212> PRT

<213> Homo sapiens

<400> 103

```

Met Tyr Met Gln Asp Tyr Trp Arg Thr Trp Leu Lys Gly Leu Arg Gly
 1          5          10          15

Phe Phe Phe Val Gly Val Leu Phe Ser Ala Val Ser Ile Ala Ala Phe
          20          25          30

Cys Thr Phe Leu Val Leu Ala Ile Thr Arg His Gln Ser Leu Thr Asp
          35          40          45

Pro Thr Ser Tyr Tyr Leu Ser Ser Val Trp Ser Phe Ile Ser Phe Lys

```

```
<400> 104
Met Gln Val Lys Asn Ser Ile His Val Thr Phe Val Ala Arg Ile Leu
  1                      5                      10                     15
Val Arg Val Leu Ile Cys Leu Ser Thr Ser Glu Ala Ile Leu Ala Arg
      20                    25                    30
Asn His Ile Tyr Val Val Ser Val Thr Asn Ala Ser Val Glu Val Gln
    35                40                45
Thr Ser
   50
```

```

<400> 105
Met Val Leu Val Phe Ala Tyr Leu Cys Val Leu Leu Ile Val Cys Trp
 1              5              10              15
Val Thr Ser Lys Thr Ser Leu Ala Leu Lys Tyr Thr Val Tyr Lys Asn
      20              25              30
Phe Lys Arg Leu Ile Trp Asn Lys Ser Ile Leu Ile Ile Thr Leu Thr
      35              40              45
Pro

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<220>
<221> SITE
<222> (550)
<223> Xaa equals any of the naturally occurring L-amino acids
```

<400> 106

```

Met Ala Thr Phe Ile Ser Val Gln Leu Lys Lys Thr Ser Glu Val Asp
 1           5           10           15
Leu Ala Lys Pro Leu Val Lys Phe Ile Gln Gln Thr Tyr Pro Ser Gly
          20           25           30
Gly Glu Glu Gln Ala Gln Tyr Cys Arg Ala Ala Glu Glu Leu Ser Lys
          35           40           45
Leu Arg Arg Ala Ala Val Gly Arg Pro Leu Asp Lys His Glu Gly Ala
          50           55           60
Leu Glu Thr Leu Leu Arg Tyr Tyr Asp Gln Ile Cys Ser Ile Glu Pro
          65           70           75           80
Lys Phe Pro Phe Ser Glu Asn Gln Ile Cys Leu Thr Phe Thr Trp Lys
          85           90           95
Asp Ala Phe Asp Lys Gly Ser Leu Phe Gly Gly Ser Val Lys Leu Ala
          100          105          110
Leu Ala Ser Leu Gly Tyr Glu Lys Ser Cys Val Leu Phe Asn Cys Ala
          115          120          125
Ala Leu Ala Ser Gln Ile Ala Ala Glu Gln Asn Leu Asp Asn Asp Glu
          130          135          140
Gly Leu Lys Ile Ala Ala Lys His Tyr Gln Phe Ala Ser Gly Ala Phe
          145          150          155          160
Leu His Ile Lys Glu Thr Val Leu Ser Ala Leu Ser Arg Glu Pro Thr
          165          170          175
Val Asp Ile Ser Pro Asp Thr Val Gly Thr Leu Ser Leu Ile Met Leu
          180          185          190
Ala Xaa Ala Gln Glu Val Phe Phe Leu Lys Ala Thr Arg Asp Lys Met
          195          200          205
Lys Asp Ala Ile Ile Ala Lys Leu Ala Asn Gln Ala Ala Asp Tyr Phe
          210          215          220
Gly Asp Ala Phe Lys Gln Cys Gln Tyr Lys Asp Thr Leu Pro Lys Glu
          225          230          235          240
Val Phe Pro Val Leu Ala Ala Lys His Cys Ile Met Gln Ala Asn Ala
          245          250          255
Glu Tyr His Gln Ser Ile Leu Ala Lys Gln Gln Lys Lys Phe Gly Glu
          260          265          270
Glu Ile Ala Arg Leu Gln His Ala Ala Glu Leu Ile Lys Thr Val Ala
          275          280          285
Ser Arg Tyr Asp Glu Tyr Val Asn Val Lys Asp Phe Ser Asp Lys Ile
          290          295          300
Asn Arg Ala Leu Xaa Ala Ala Lys Lys Asp Asn Asp Phe Ile Tyr His
          305          310          315          320
Asp Arg Val Pro Asp Leu Lys Asp Leu Asp Pro Ile Gly Lys Ala Thr
          325          330          335
Leu Val Lys Ser Thr Pro Val Asn Val Pro Ile Ser Gln Lys Phe Thr

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340					345					350					
Asp	Leu	Phe	Glu	Lys	Met	Val	Pro	Val	Ser	Val	Gln	Gln	Ser	Leu	Ala
		355					360					365			
Ala	Tyr	Asn	Gln	Arg	Lys	Ala	Asp	Leu	Val	Asn	Arg	Ser	Ile	Ala	Gln
	370					375					380				
Met	Arg	Glu	Ala	Thr	Thr	Leu	Ala	Asn	Gly	Val	Leu	Ala	Ser	Leu	Asn
385						390					395				400
Leu	Pro	Ala	Ala	Ile	Glu	Asp	Val	Ser	Gly	Asp	Thr	Val	Pro	Gln	Ser
				405					410					415	
Ile	Leu	Thr	Lys	Ser	Arg	Ser	Val	Ile	Glu	Gln	Gly	Gly	Ile	Gln	Thr
			420					425					430		
Val	Asp	Gln	Leu	Ile	Lys	Glu	Leu	Pro	Glu	Leu	Leu	Gln	Arg	Asn	Arg
		435					440					445			
Glu	Ile	Leu	Asp	Glu	Ser	Leu	Arg	Leu	Leu	Asp	Glu	Glu	Glu	Ala	Thr
	450					455					460				
Asp	Asn	Asp	Leu	Arg	Ala	Lys	Phe	Lys	Glu	Arg	Trp	Gln	Arg	Thr	Pro
465						470					475				480
Ser	Asn	Glu	Leu	Tyr	Lys	Pro	Leu	Arg	Ala	Glu	Gly	Thr	Asn	Phe	Arg
				485					490					495	
Thr	Val	Leu	Asp	Lys	Ala	Val	Gln	Ala	Asp	Gly	Gln	Val	Lys	Glu	Cys
			500					505					510		
Tyr	Gln	Ser	His	Arg	Asp	Thr	Ile	Val	Leu	Leu	Cys	Lys	Pro	Glu	Pro
		515					520					525			
Glu	Leu	Asn	Ala	Ala	Ile	Pro	Ser	Ala	Asn	Pro	Ala	Lys	Thr	Met	Gln
	530					535					540				
Gly	Ser	Glu	Val	Val	Xaa	Val	Leu	Lys	Ser	Leu	Leu	Ser	Asn	Leu	Asp
545						550					555				560
Glu	Val	Lys	Lys	Glu	Arg	Glu	Gly	Leu	Glu	Asn	Asp	Leu	Lys	Ser	Val
				565					570					575	
Asn	Phe	Asp	Met	Thr	Ser	Lys	Phe	Leu	Thr	Ala	Leu	Ala	Gln	Asp	Gly
			580					585					590		
Val	Ile	Asn	Glu	Glu	Ala	Leu	Ser	Val	Thr	Glu	Leu	Asp	Arg	Val	Tyr
		595					600					605			
Gly	Gly	Leu	Thr	Thr	Lys	Val	Gln	Glu	Ser	Leu	Lys	Lys	Gln	Glu	Gly
	610					615					620				
Leu	Leu	Lys	Asn	Ile	Gln	Val	Ser	His	Gln	Glu	Phe	Ser	Lys	Met	Lys
625						630					635				640
Gln	Ser	Asn	Asn	Glu	Ala	Asn	Leu	Arg	Glu	Glu	Val	Leu	Lys	Asn	Leu
				645					650					655	
Ala	Thr	Ala	Tyr	Asp	Asn	Phe	Val	Glu	Leu	Val	Ala	Asn	Leu	Lys	Glu
			660					665					670		
Gly	Thr	Lys	Phe	Tyr	Asn	Glu	Leu	Thr	Glu	Ile	Leu	Val	Arg	Phe	Gln
		675					680					685			
Asn	Lys	Cys	Ser	Asp	Ile	Val	Phe	Ala	Arg	Lys	Thr	Glu	Arg	Asp	Glu

690 695 700
 Leu Leu Lys Asp Leu Gln Gln Ser Ile Ala Arg Glu Pro Ser Ala Pro
 705 710 715 720
 Ser Ile Pro Thr Pro Ala Tyr Gln Ser Leu Pro Ala Gly Gly His Ala
 725 730 735
 Pro Thr Pro Pro Thr Pro Ala Pro Arg Thr Met Pro Pro Thr Lys Pro
 740 745 750
 Gln Pro Pro Ala Arg Pro Pro Pro Pro Val Leu Pro Ala Asn Arg Ala
 755 760 765
 Pro Ser Ala Thr Ala Pro Ser Pro Val Gly Ala Gly Thr Ala Ala Pro
 770 775 780
 Ala Pro Ser Gln Thr Pro Gly Ser Ala Pro Pro Pro Gln Ala Gln Gly
 785 790 795 800
 Pro Pro Tyr Pro Thr Tyr Pro Gly Tyr Pro Gly Tyr Cys Gln Met Pro
 805 810 815
 Met Pro Met Gly Tyr Asn Pro Tyr Ala Tyr Gly Gln Tyr Asn Met Pro
 820 825 830
 Tyr Pro Pro Val Tyr His Gln Ser Pro Gly Gln Ala Pro Tyr Pro Gly
 835 840 845
 Pro Gln Gln Pro Ser Tyr Pro Phe Pro Gln Pro Pro Gln Gln Ser Tyr
 850 855 860
 Tyr Pro Gln Gln
 865

<210> 107
 <211> 56
 <212> PRT
 <213> Homo sapiens

<400> 107
 Met Arg Gly His Ile Thr Thr Leu Leu Thr Thr Ser Phe Leu Val Phe
 1 5 10 15
 Gly Leu His Ile Ile Phe Phe Leu Asn Ile Ser Cys Phe Asn Phe Arg
 20 25 30
 Val Phe Ile Leu Phe Glu Thr Arg Pro Glu Asp Ser Arg Leu Tyr Arg
 35 40 45
 Glu Arg Pro Val Leu Pro Arg Tyr
 50 55

<210> 108
 <211> 110
 <212> PRT
 <213> Homo sapiens

<400> 108
 Met Glu Phe Pro Gly Ala Asp Gly Cys Asn Gln Val Asp Ala Glu Tyr
 1 5 10 15
 Leu Lys Val Gly Ser Glu Gly His Phe Arg Val Pro Ala Leu Gly Tyr
 20 25 30

Leu Asp Val Arg Ile Val Asp Thr Asp Tyr Ser Ser Phe Ala Val Leu
 35 40 45
 Tyr Ile Tyr Lys Glu Leu Glu Gly Ala Leu Ser Thr Met Val Gln Leu
 50 55 60
 Tyr Ser Arg Thr Gln Asp Val Ser Pro Gln Ala Leu Lys Ala Phe Gln
 65 70 75 80
 Asp Phe Tyr Pro Thr Leu Gly Leu Pro Glu Asp Met Met Val Met Leu
 85 90 95
 Pro Gln Ser Asp Ala Cys Asn Pro Glu Ser Lys Glu Ala Pro
 100 105 110

<210> 109

<211> 334

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (105)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 109

Met Glu Pro Gly Pro Thr Ala Ala Gln Arg Arg Cys Ser Leu Pro Pro
 1 5 10 15

Trp Leu Pro Leu Gly Leu Leu Leu Trp Ser Gly Leu Ala Leu Gly Ala
 20 25 30

Leu Pro Phe Gly Ser Ser Pro His Arg Val Phe His Asp Leu Leu Ser
 35 40 45

Glu Gln Gln Leu Leu Glu Val Glu Asp Leu Ser Leu Ser Leu Leu Gln
 50 55 60

Gly Gly Gly Leu Gly Pro Leu Ser Leu Pro Pro Asp Leu Pro Asp Leu
 65 70 75 80

Asp Pro Glu Cys Arg Glu Leu Leu Leu Asp Phe Ala Asn Ser Ser Ala
 85 90 95

Glu Leu Thr Gly Cys Leu Val Arg Xaa Ala Arg Pro Val Arg Leu Cys
 100 105 110

Gln Thr Cys Tyr Pro Leu Phe Gln Gln Val Val Ser Lys Met Asp Asn
 115 120 125

Ile Ser Arg Ala Ala Gly Asn Thr Ser Glu Ser Gln Ser Cys Ala Arg
 130 135 140

Ser Leu Leu Met Ala Asp Arg Met Gln Ile Val Val Ile Leu Ser Glu
 145 150 155 160

Phe Phe Asn Thr Thr Trp Gln Glu Ala Asn Cys Ala Asn Cys Leu Thr
 165 170 175

Asn Asn Ser Glu Glu Leu Ser Asn Ser Thr Val Tyr Phe Leu Asn Leu
 180 185 190

Phe Asn His Thr Leu Thr Cys Phe Glu His Asn Leu Gln Gly Asn Ala
 195 200 205

His Ser Leu Leu Gln Thr Lys Asn Tyr Ser Glu Val Cys Lys Asn Cys
 210 215 220
 Arg Glu Ala Tyr Lys Thr Leu Ser Ser Leu Tyr Ser Glu Met Gln Lys
 225 230 235 240
 Met Asn Glu Leu Glu Asn Lys Ala Glu Pro Gly Thr His Leu Cys Ile
 245 250 255
 Asp Val Glu Asp Ala Met Asn Ile Thr Arg Lys Leu Trp Ser Arg Thr
 260 265 270
 Phe Asn Cys Ser Val Pro Cys Ser Asp Thr Val Pro Val Ile Ala Val
 275 280 285
 Ser Val Phe Ile Leu Phe Leu Pro Val Val Phe Tyr Leu Ser Ser Phe
 290 295 300
 Leu His Ser Glu Gln Lys Lys Arg Lys Leu Ile Leu Pro Lys Arg Leu
 305 310 315 320
 Lys Ser Ser Thr Ser Phe Ala Asn Ile Gln Glu Asn Ser Asn
 325 330

<210> 110
 <211> 75
 <212> PRT
 <213> Homo sapiens

<400> 110
 Met Ser Leu Ser Ile Leu Val Ala Leu Ser Leu Gln Ile Leu Phe Leu
 1 5 10 15
 Phe Thr Ile Leu Lys Cys Met Leu Ala Lys Trp Val Asp Phe Gln Ile
 20 25 30
 Lys Cys Ser Phe His Lys Ser Phe Val Met Val Phe Trp Ser Glu Met
 35 40 45
 His Phe His Phe Ser Phe Leu Phe Leu Leu Ser Ile Leu Ser Phe Phe
 50 55 60
 Pro Asn Lys Ile Tyr Pro Gly Asp Tyr Ile Cys
 65 70 75

<210> 111
 <211> 363
 <212> PRT
 <213> Homo sapiens

<400> 111
 Met Ala Ala Val Leu Thr Trp Ala Leu Ala Leu Leu Ser Ala Phe Ser
 1 5 10 15
 Ala Thr Gln Ala Arg Lys Gly Phe Trp Asp Tyr Phe Ser Gln Thr Ser
 20 25 30
 Gly Asp Lys Gly Arg Val Glu Gln Ile His Gln Gln Lys Met Ala Arg
 35 40 45
 Glu Pro Ala Thr Leu Lys Asp Ser Leu Glu Gln Asp Leu Asn Asn Met
 50 55 60

78

Asn Lys Phe Leu Glu Lys Leu Arg Pro Leu Ser Gly Ser Glu Ala Pro
 65 70 75 80
 Arg Leu Pro Gln Asp Pro Val Gly Met Arg Arg Gln Leu Gln Glu Glu
 85 90 95
 Leu Glu Glu Val Lys Ala Arg Leu Gln Pro Tyr Met Ala Glu Ala His
 100 105 110
 Glu Leu Val Gly Trp Asn Leu Glu Gly Leu Arg Gln Gln Leu Lys Pro
 115 120 125
 Tyr Thr Met Asp Leu Met Glu Gln Val Ala Leu Arg Val Gln Glu Leu
 130 135 140
 Gln Glu Gln Leu Arg Val Val Gly Glu Asp Thr Lys Ala Gln Leu Leu
 145 150 155 160
 Gly Gly Val Asp Glu Ala Trp Ala Leu Leu Gln Gly Leu Gln Ser Arg
 165 170 175
 Val Val His His Thr Gly Arg Phe Lys Glu Leu Phe His Pro Tyr Ala
 180 185 190
 Glu Ser Leu Val Ser Gly Ile Gly Arg His Val Gln Glu Leu His Arg
 195 200 205
 Ser Val Ala Pro His Ala Pro Ala Ser Pro Ala Arg Leu Ser Arg Cys
 210 215 220
 Val Gln Val Leu Ser Arg Lys Leu Thr Leu Lys Ala Lys Ala Leu His
 225 230 235 240
 Ala Arg Ile Gln Gln Asn Leu Asp Gln Leu Arg Glu Glu Leu Ile Arg
 245 250 255
 Ala Phe Ala Gly Thr Gly Thr Glu Glu Gly Ala Gly Pro Asp Pro Gln
 260 265 270
 Met Leu Ser Glu Glu Val Arg Gln Arg Leu Gln Ala Phe Arg Gln Asp
 275 280 285
 Thr Tyr Leu Gln Ile Ala Ala Phe Thr Arg Ala Ile Asp Gln Glu Thr
 290 295 300
 Glu Glu Val Gln Gln Gln Leu Ala Pro Pro Pro Gly His Ser Ala
 305 310 315 320
 Phe Ala Pro Glu Phe Gln Gln Thr Asp Ser Gly Lys Val Leu Ser Lys
 325 330 335
 Leu Gln Ala Arg Leu Asp Asp Leu Trp Glu Asp Ile Thr His Ser Leu
 340 345 350
 His Asp Gln Gly His Ser His Leu Gly Asp Pro
 355 360

<210> 112
 <211> 530
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (488)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (490)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (494)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (495)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (505)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 112

Met Glu Phe Gly Leu Thr Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1 5 10 15

Val His Cys Gln Val Gln Leu Val Glu Ser Gly Gly Ala Val Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Arg Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Gln Trp Leu Ala Leu Val Leu His Asp Gly Gly Gln Lys Tyr Asn Glu
65 70 75 80

Asp Val Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Asn Asn
85 90 95

Lys Val Tyr Leu Gln Met Asp Ser Leu Arg Gly Glu Asp Thr Ala Thr
100 105 110

Tyr Tyr Cys Val Arg Gly Met Trp Glu Gln Leu Pro Ser Tyr Tyr Phe
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Pro
130 135 140

Thr Ser Pro Lys Val Phe Pro Leu Ser Leu Cys Ser Thr Gln Pro Asp
145 150 155 160

Gly Asn Val Val Ile Ala Cys Leu Val Gln Gly Phe Phe Pro Gln Glu
165 170 175

Pro Leu Ser Val Thr Trp Ser Glu Ser Gly Gln Gly Val Thr Ala Arg
180 185 190

Asn Phe Pro Pro Ser Gln Asp Ala Ser Gly Asp Leu Tyr Thr Thr Ser
195 200 205

Ser Gln Leu Thr Leu Pro Ala Thr Gln Cys Leu Ala Gly Lys Ser Val
210 215 220

Thr Cys His Val Lys His Tyr Thr Asn Pro Ser Gln Asp Val Thr Val

80

225		230		235		240
Pro Cys Pro Val	Pro Ser Thr	Pro Pro Thr	Pro Ser Pro Ser	Thr Pro		
	245			250		255
Pro Thr Pro Ser	Pro Ser Cys Cys	His Pro Arg Leu	Ser Leu His Arg			
	260	265	270			
Pro Ala Leu Glu Asp	Leu Leu Leu Gly	Ser Glu Ala Asn	Leu Thr Cys			
	275	280	285			
Thr Leu Thr Gly Leu	Arg Asp Ala Ser	Gly Val Thr Phe	Thr Trp Thr			
	290	295	300			
Pro Ser Ser Gly Lys	Ser Ala Val Gln	Gly Pro Pro Asp	Arg Asp Leu			
305	310	315	320			
Cys Gly Cys Tyr	Ser Val Ser Ser	Val Leu Pro Gly	Cys Ala Glu Pro			
	325	330	335			
Trp Asn His Gly Lys	Thr Phe Thr Cys	Thr Ala Ala Tyr	Pro Glu Ser			
	340	345	350			
Lys Thr Pro Leu Thr	Ala Thr Leu Ser	Lys Ser Gly Asn	Thr Phe Arg			
	355	360	365			
Pro Glu Val His Leu	Leu Pro Pro Pro	Ser Glu Glu Leu	Ala Leu Asn			
	370	375	380			
Glu Leu Val Thr Leu	Thr Cys Leu Ala	Arg Gly Phe Ser	Pro Lys Asp			
385	390	395	400			
Val Leu Val Arg Trp	Leu Gln Gly Ser	Gln Glu Leu Pro	Arg Glu Lys			
	405	410	415			
Tyr Leu Thr Trp Ala	Ser Arg Gln Glu	Pro Ser Gln Gly	Thr Thr Thr			
	420	425	430			
Phe Ala Val Thr Ser	Ile Leu Arg Val	Ala Ala Glu Asp	Trp Lys Lys			
	435	440	445			
Gly Asp Thr Phe Ser	Cys Met Val Gly	His Glu Ala Leu	Pro Leu Ala			
	450	455	460			
Phe Thr Gln Lys Thr	Ile Asp Arg Leu	Ala Gly Lys Pro	Thr His Val			
465	470	475	480			
Asn Val Ser Val Val	Met Ala Xaa Val	Xaa Gly Pro Cys	Xaa Xaa Ala			
	485	490	495			
Ala Arg Leu Ser Pro	Pro Leu Asn Xaa	Leu His Ala Pro	Pro Lys Lys			
	500	505	510			
Lys Lys Lys Lys Lys	Lys Lys Lys Lys	Lys Lys Lys Lys	Lys Lys Lys Lys			
	515	520	525			
Lys Lys						
530						

<210> 113

<211> 207

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (75)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (77)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (112)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 113

Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu
1 5 10 15

Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys
20 25 30

Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp
35 40 45

Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Pro Ala
50 55 60

Ile Pro Gly Ile Arg Gly Pro Lys Gly Gln Xaa Gly Xaa Ala Glu Ile
65 70 75 80

Pro Val Ser Val His Gly His Ser Ala Asp Pro Pro Ala Pro Cys Thr
85 90 95

Gln Gln Pro Asp Gln Ile Gln Arg Gly Pro His Gln Pro Ala Glu Xaa
100 105 110

Tyr Asp Thr Ser Thr Gly Lys Phe Thr Cys Lys Val Pro Gly Leu Tyr
115 120 125

Tyr Phe Val Tyr His Ala Ser His Thr Ala Asn Leu Cys Val Leu Leu
130 135 140

Tyr Arg Ser Gly Val Lys Val Val Thr Phe Cys Gly His Thr Ser Lys
145 150 155 160

Thr Asn Gln Val Asn Ser Gly Gly Val Leu Leu Arg Leu Gln Val Gly
165 170 175

Glu Glu Val Trp Leu Ala Val Asn Asp Tyr Tyr Asp Met Val Gly Ile
180 185 190

Gln Gly Ser Asp Ser Val Phe Ser Gly Phe Leu Leu Phe Pro Asp
195 200 205

<210> 114

<211> 287

<212> PRT

<213> Homo sapiens

<400> 114

Met Gly Ala Leu Arg Pro Thr Leu Leu Pro Pro Ser Leu Pro Leu Leu
1 5 10 15

Leu Leu Leu Met Leu Gly Met Gly Cys Trp Ala Arg Glu Val Leu Val
20 25 30

Pro Glu Gly Pro Leu Tyr Arg Val Ala Gly Thr Ala Val Ser Ile Ser
 35 40 45
 Cys Asn Val Thr Gly Tyr Glu Gly Pro Ala Gln Gln Asn Phe Glu Trp
 50 55 60
 Phe Leu Tyr Arg Pro Glu Ala Pro Asp Thr Ala Leu Gly Ile Val Ser
 65 70 75 80
 Thr Lys Asp Thr Gln Phe Ser Tyr Ala Val Phe Lys Ser Arg Val Val
 85 90 95
 Ala Gly Glu Val Gln Val Gln Arg Leu Gln Gly Asp Ala Val Val Leu
 100 105 110
 Lys Ile Ala Arg Leu Gln Ala Gln Asp Ala Gly Ile Tyr Glu Cys His
 115 120 125
 Thr Pro Ser Thr Asp Thr Arg Tyr Leu Gly Ser Tyr Ser Gly Lys Val
 130 135 140
 Glu Leu Arg Val Leu Pro Asp Val Leu Gln Val Ser Ala Ala Pro Pro
 145 150 155 160
 Gly Pro Arg Gly Arg Gln Ala Pro Thr Ser Pro Pro Arg Met Thr Val
 165 170 175
 His Glu Gly Gln Glu Leu Ala Leu Gly Cys Leu Ala Arg Thr Ser Thr
 180 185 190
 Gln Lys His Thr His Leu Ala Val Ser Phe Gly Arg Ser Val Pro Glu
 195 200 205
 Ala Pro Val Gly Arg Ser Thr Leu Gln Glu Val Val Gly Ile Arg Ser
 210 215 220
 Asp Leu Ala Val Glu Ala Gly Ala Pro Tyr Ala Glu Arg Leu Ala Ala
 225 230 235 240
 Gly Glu Leu Arg Leu Gly Lys Glu Gly Thr Asp Arg Tyr Arg Met Val
 245 250 255
 Val Gly Gly Ala Gln Ala Gly Asp Ala Gly Thr Tyr His Cys Thr Ala
 260 265 270
 Ala Glu Trp Ile Gln Asp Pro Asp Gly Ser Trp Ala Gln Ile Ala
 275 280 285

<210> 115

<211> 245

<212> PRT

<213> Homo sapiens

<400> 115

Met Glu Gly Pro Arg Gly Trp Leu Val Leu Cys Val Leu Ala Ile Ser
 1 5 10 15

Leu Ala Ser Met Val Thr Glu Asp Leu Cys Arg Ala Pro Asp Gly Lys
 20 25 30

Lys Gly Glu Ala Gly Arg Pro Gly Arg Arg Gly Arg Pro Gly Leu Lys
 35 40 45

Gly Glu Gln Gly Glu Pro Gly Ala Pro Gly Ile Arg Thr Gly Ile Gln

83

50 55 60
 Gly Leu Lys Gly Asp Gln Gly Glu Pro Gly Pro Ser Gly Asn Pro Gly
 65 70 75 80
 Lys Val Gly Tyr Pro Gly Pro Ser Gly Pro Leu Gly Ala Arg Gly Ile
 85 90 95
 Pro Gly Ile Lys Gly Thr Lys Gly Ser Pro Gly Asn Ile Lys Asp Gln
 100 105 110
 Pro Arg Pro Ala Phe Ser Ala Ile Arg Arg Asn Pro Pro Met Gly Gly
 115 120 125
 Asn Val Val Ile Phe Asp Thr Val Ile Thr Asn Gln Glu Glu Pro Tyr
 130 135 140
 Gln Asn His Ser Gly Arg Phe Val Cys Thr Val Pro Gly Tyr Tyr Tyr
 145 150 155 160
 Phe Thr Phe Gln Val Leu Ser Gln Trp Glu Ile Cys Leu Ser Ile Val
 165 170 175
 Ser Ser Ser Arg Gly Gln Val Arg Arg Ser Leu Gly Phe Cys Asp Thr
 180 185 190
 Thr Asn Lys Gly Leu Phe Gln Val Val Ser Gly Gly Met Val Leu Gln
 195 200 205
 Leu Gln Gln Gly Asp Gln Val Trp Val Glu Lys Asp Pro Lys Lys Gly
 210 215 220
 His Ile Tyr Gln Gly Ser Glu Ala Asp Ser Val Phe Ser Gly Phe Leu
 225 230 235 240
 Ile Phe Pro Ser Ala
 245

<210> 116

<211> 245

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (128)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 116

Met Glu Gly Pro Arg Gly Trp Leu Val Leu Cys Val Leu Ala Ile Ser
 1 5 10 15

Leu Ala Ser Met Val Thr Glu Asp Leu Cys Arg Ala Pro Asp Gly Lys
 20 25 30

Lys Gly Glu Ala Gly Arg Pro Gly Arg Arg Gly Arg Pro Gly Leu Lys
 35 40 45

Gly Glu Gln Gly Glu Pro Gly Ala Pro Gly Ile Arg Thr Gly Ile Gln
 50 55 60

Gly Leu Lys Gly Asp Gln Gly Glu Pro Gly Pro Ser Gly Asn Pro Gly
 65 70 75 80

Lys Val Gly Tyr Pro Gly Pro Ser Gly Pro Leu Gly Ala Arg Gly Ile

84

85										90					95				
Pro	Gly	Ile	Lys	Gly	Thr	Lys	Gly	Ser	Pro	Gly	Asn	Ile	Lys	Asp	Gln				
			100					105					110						
Pro	Arg	Pro	Ala	Phe	Ser	Ala	Ile	Arg	Arg	Asn	Pro	Pro	Met	Gly	Xaa				
		115					120					125							
Asn	Val	Val	Ile	Phe	Asp	Thr	Val	Ile	Thr	Asn	Gln	Glu	Glu	Pro	Tyr				
	130					135					140								
Gln	Asn	His	Ser	Gly	Arg	Phe	Val	Cys	Thr	Val	Pro	Gly	Tyr	Tyr	Tyr				
145					150					155					160				
Phe	Thr	Phe	Gln	Val	Leu	Ser	Gln	Trp	Glu	Ile	Cys	Leu	Ser	Ile	Val				
			165						170					175					
Ser	Ser	Ser	Arg	Gly	Gln	Val	Arg	Arg	Ser	Leu	Gly	Phe	Cys	Asp	Thr				
			180					185					190						
Thr	Asn	Lys	Gly	Leu	Phe	Gln	Val	Val	Ser	Gly	Gly	Met	Val	Leu	Gln				
		195					200					205							
Leu	Gln	Gln	Gly	Asp	Gln	Val	Trp	Val	Glu	Lys	Asp	Pro	Lys	Lys	Gly				
	210					215					220								
His	Ile	Tyr	Gln	Gly	Ser	Glu	Ala	Asp	Ser	Val	Phe	Ser	Gly	Phe	Leu				
225					230					235					240				
Ile	Phe	Pro	Ser	Ala															
				245															

<210> 117

<211> 229

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (47)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (49)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 117

Met	Glu	Gly	Pro	Arg	Gly	Trp	Leu	Val	Leu	Cys	Val	Leu	Ala	Ile	Ser				
1				5					10					15					

Leu	Ala	Ser	Met	Val	Thr	Glu	Asp	Leu	Cys	Arg	Ala	Pro	Asp	Gly	Lys				
			20					25					30						

Lys	Gly	Glu	Ala	Gly	Arg	Pro	Gly	Arg	Arg	Gly	Arg	Pro	Gly	Xaa	Lys				
	35						40					45							

Xaa	Leu	Lys	Gly	Asp	Gln	Gly	Glu	Pro	Gly	Pro	Ser	Gly	Asn	Pro	Gly				
	50					55					60								

Lys	Val	Gly	Tyr	Pro	Gly	Pro	Ser	Gly	Pro	Leu	Gly	Ala	Arg	Gly	Ile				
65					70					75					80				

Pro	Gly	Ile	Lys	Gly	Thr	Lys	Gly	Ser	Pro	Gly	Asn	Ile	Lys	Asp	Gln				
				85					90					95					

Pro Arg Pro Ala Phe Ser Ala Ile Arg Arg Asn Pro Pro Met Gly Gly
 100 105 110
 Asn Val Val Ile Phe Asp Thr Val Ile Thr Asn Gln Glu Glu Pro Tyr
 115 120 125
 Gln Asn His Ser Gly Arg Phe Val Cys Thr Val Pro Gly Tyr Tyr Tyr
 130 135 140
 Phe Thr Phe Gln Val Leu Ser Gln Trp Glu Ile Cys Leu Ser Ile Val
 145 150 155 160
 Ser Ser Ser Arg Gly Gln Val Arg Arg Ser Leu Gly Phe Cys Asp Thr
 165 170 175
 Thr Asn Lys Gly Leu Phe Gln Val Val Ser Gly Gly Met Val Leu Gln
 180 185 190
 Leu Gln Gln Gly Asp Gln Val Trp Val Glu Lys Asp Pro Lys Lys Gly
 195 200 205
 His Ile Tyr Gln Gly Ser Glu Ala Asp Ser Val Phe Ser Gly Phe Leu
 210 215 220
 Ile Phe Pro Ser Ala
 225

<210> 118
 <211> 245
 <212> PRT
 <213> Homo sapiens

<400> 118
 Met Glu Gly Pro Arg Gly Trp Leu Val Leu Cys Val Leu Ala Ile Ser
 1 5 10 15
 Leu Ala Ser Met Val Thr Glu Asp Leu Cys Arg Ala Pro Asp Gly Lys
 20 25 30
 Lys Gly Glu Ala Gly Arg Pro Gly Arg Arg Gly Arg Pro Gly Leu Lys
 35 40 45
 Gly Glu Gln Gly Glu Pro Gly Ala Pro Gly Ile Arg Thr Gly Ile Gln
 50 55 60
 Gly Leu Lys Gly Asp Gln Gly Glu Pro Gly Pro Ser Gly Asn Pro Gly
 65 70 75 80
 Lys Val Gly Tyr Pro Gly Pro Ser Gly Pro Leu Gly Ala Arg Gly Ile
 85 90 95
 Pro Gly Ile Lys Gly Thr Lys Gly Ser Pro Gly Asn Ile Lys Asp Gln
 100 105 110
 Pro Arg Pro Ala Phe Ser Ala Ile Arg Arg Asn Pro Pro Met Gly Gly
 115 120 125
 Asn Val Val Ile Phe Asp Thr Val Ile Thr Asn Gln Glu Glu Pro Tyr
 130 135 140
 Gln Asn His Ser Gly Arg Phe Val Cys Thr Val Pro Gly Tyr Tyr Tyr
 145 150 155 160
 Phe Thr Phe Gln Val Leu Ser Gln Trp Glu Ile Cys Leu Ser Ile Val

175

<400>	119															
Met	Glu	Gly	Pro	Arg	Gly	Trp	Leu	Val	Leu	Cys	Val	Leu	Ala	Ile	Ser	
1				5					10					15		
Leu	Ala	Ser	Met	Val	Thr	Glu	Asp	Leu	Cys	Arg	Ala	Pro	Asp	Gly	Lys	
			20					25					30			
Lys	Gly	Glu	Ala	Gly	Arg	Pro	Gly	Arg	Arg	Gly	Arg	Pro	Gly	Leu	Lys	
		35					40					45				
Gly	Glu	Gln	Gly	Glu	Pro	Gly	Ala	Pro	Gly	Ile	Arg	Thr	Gly	Ile	Gln	
	50					55					60					
Gly	Leu	Lys	Gly	Asp	Gln	Gly	Glu	Pro	Gly	Pro	Ser	Gly	Asn	Pro	Gly	
65					70					75					80	
Lys	Val	Gly	Tyr	Pro	Gly	Pro	Ser	Gly	Pro	Leu	Gly	Ala	Arg	Gly	Ile	
				85					90					95		
Pro	Gly	Ile	Lys	Gly	Thr	Lys	Gly	Ser	Pro	Gly	Asn	Ile	Lys	Asp	Gln	
			100					105					110			
Pro	Arg	Pro	Ala	Phe	Ser	Ala	Ile	Arg	Arg	Asn	Pro	Pro	Met	Gly	Gly	
		115					120					125				
Asn	Val	Val	Ile	Phe	Asp	Thr	Val	Ile	Thr	Asn	Gln	Glu	Glu	Pro	Tyr	
	130					135					140					
Gln	Asn	His	Ser	Gly	Arg	Phe	Val	Cys	Thr	Val	Pro	Gly	Tyr	Tyr	Tyr	
145					150					155					160	
Phe	Thr	Phe	Gln	Val	Leu	Ser	Gln	Trp	Glu	Ile	Cys	Leu	Ser	Ile	Val	
				165					170					175		
Ser	Ser	Ser	Arg	Gly	Gln	Val	Arg	Arg	Ser	Leu	Gly	Phe	Cys	Asp	Thr	
			180					185					190			
Thr	Asn	Lys	Gly	Leu	Phe	Gln	Val	Val	Ser	Gly	Gly	Met	Val	Leu	Gln	
		195					200					205				
Leu	Gln	Gln	Gly	Asp	Gln	Val	Trp	Val	Glu	Lys	Asp	Pro	Lys	Lys	Gly	
	210					215					220					

87

His Ile Tyr Gln Gly Ser Glu Ala Asp Ser Val Phe Ser Gly Phe Leu
 225 230 235 240

Ile Phe Pro Ser Ala
 245

<210> 120
 <211> 32
 <212> PRT
 <213> Homo sapiens

<400> 120
 Met Gly Val Asn Lys Val Leu Phe Thr Phe Phe Phe Ser Ser Leu
 1 5 10 15
 Leu Asp Gly Val Gly Thr Ser His Ser Leu Ala Ser Phe Pro His Thr
 20 25 30

<210> 121
 <211> 298
 <212> PRT
 <213> Homo sapiens

<400> 121
 Met Lys Thr Leu Gln Ser Thr Leu Leu Leu Leu Leu Val Pro Leu
 1 5 10 15
 Ile Lys Pro Ala Pro Pro Thr Gln Gln Asp Ser Arg Ile Ile Tyr Asp
 20 25 30
 Tyr Gly Thr Asp Asn Phe Glu Glu Ser Ile Phe Ser Gln Asp Tyr Glu
 35 40 45
 Asp Lys Tyr Leu Asp Gly Lys Asn Ile Lys Glu Lys Glu Thr Val Ile
 50 55 60
 Ile Pro Asn Glu Lys Ser Leu Gln Leu Gln Lys Asp Glu Ala Ile Thr
 65 70 75 80
 Pro Leu Pro Pro Lys Lys Glu Asn Asp Glu Met Pro Thr Cys Leu Leu
 85 90 95
 Cys Val Cys Leu Ser Gly Ser Val Tyr Cys Glu Glu Val Asp Ile Asp
 100 105 110
 Ala Val Pro Pro Leu Pro Lys Glu Ser Ala Tyr Leu Tyr Ala Arg Phe
 115 120 125
 Asn Lys Ile Lys Lys Leu Thr Ala Lys Asp Phe Ala Asp Ile Pro Asn
 130 135 140
 Leu Arg Arg Leu Asp Phe Thr Gly Asn Leu Ile Glu Asp Ile Glu Asp
 145 150 155 160
 Gly Thr Phe Ser Lys Leu Ser Leu Leu Glu Leu Ser Leu Ala Glu
 165 170 175
 Asn Gln Leu Leu Lys Leu Pro Val Leu Pro Pro Lys Leu Thr Leu Phe
 180 185 190
 Asn Ala Lys Tyr Asn Lys Ile Lys Ser Arg Gly Ile Lys Ala Asn Ala

195 200 205
 Phe Lys Lys Leu Asn Asn Leu Thr Phe Leu Tyr Leu Asp His Asn Ala
 210 215 220
 Leu Glu Ser Val Pro Leu Asn Leu Pro Glu Ser Leu Arg Val Ile His
 225 230 235 240
 Leu Gln Phe Asn Asn Ile Ala Ser Ile Thr Asp Asp Thr Phe Cys Lys
 245 250 255
 Ala Asn Asp Thr Ser Tyr Ile Arg Asp Arg Ile Glu Glu Ile Arg Leu
 260 265 270
 Glu Gly Asn Pro Ile Val Leu Gly Lys His Pro Asn Ser Phe Ile Cys
 275 280 285
 Leu Lys Arg Leu Pro Ile Gly Ser Tyr Phe
 290 295

<210> 122
 <211> 55
 <212> PRT
 <213> Homo sapiens

<400> 122
 Met Cys Leu Leu Gly Gly Leu Ser Ala Pro Pro Leu Leu Leu Leu Pro
 1 5 10 15
 Leu Leu Pro Leu Leu Leu Cys Pro Pro Thr Gly Arg Val Thr Ala Ala
 20 25 30
 Phe Pro Gln Ser Tyr Leu Met Pro Tyr Lys Val Trp Val Thr Asn Arg
 35 40 45
 Val Phe Leu Lys Asn Ser Gln
 50 55

<210> 123
 <211> 19
 <212> PRT
 <213> Homo sapiens

<400> 123
 Glu Cys Cys Glu Thr Ala Ala Pro Pro Gly Pro His Arg Arg Pro Glu
 1 5 10 15
 Ser Gly Gln

<210> 124
 <211> 514
 <212> PRT
 <213> Homo sapiens

<400> 124
 Glu Leu Cys Arg Gln Pro Lys Pro Ser Thr Val Gln Ala Cys Asn Arg
 1 5 10 15
 Phe Asn Cys Pro Pro Ala Trp Tyr Pro Ala Gln Trp Gln Pro Cys Ser
 20 25 30
 Arg Thr Cys Gly Gly Gly Val Gln Lys Arg Glu Val Leu Cys Lys Gln

35					40					45					
Arg	Met	Ala	Asp	Gly	Ser	Phe	Leu	Glu	Leu	Pro	Glu	Thr	Phe	Cys	Ser
50					55					60					
Ala	Ser	Lys	Pro	Ala	Cys	Gln	Gln	Ala	Cys	Lys	Lys	Asp	Asp	Cys	Pro
65					70					75					80
Ser	Glu	Trp	Leu	Leu	Ser	Asp	Trp	Thr	Glu	Cys	Ser	Thr	Ser	Cys	Gly
				85					90					95	
Glu	Gly	Thr	Gln	Thr	Arg	Ser	Ala	Ile	Cys	Arg	Lys	Met	Leu	Lys	Thr
			100					105					110		
Gly	Leu	Ser	Thr	Val	Val	Asn	Ser	Thr	Leu	Cys	Pro	Pro	Leu	Pro	Phe
		115					120					125			
Ser	Ser	Ser	Ile	Arg	Pro	Cys	Met	Leu	Ala	Thr	Cys	Ala	Arg	Pro	Gly
		130				135					140				
Arg	Pro	Ser	Thr	Lys	His	Ser	Pro	His	Ile	Ala	Ala	Ala	Arg	Lys	Val
145					150					155					160
Tyr	Ile	Gln	Thr	Arg	Arg	Gln	Arg	Lys	Leu	His	Phe	Val	Val	Gly	Gly
				165					170					175	
Phe	Ala	Tyr	Leu	Leu	Pro	Lys	Thr	Ala	Val	Val	Leu	Arg	Cys	Pro	Ala
			180					185					190		
Arg	Arg	Val	Arg	Lys	Pro	Leu	Ile	Thr	Trp	Glu	Lys	Asp	Gly	Gln	His
		195					200					205			
Leu	Ile	Ser	Ser	Thr	His	Val	Thr	Val	Ala	Pro	Phe	Gly	Tyr	Leu	Lys
	210					215					220				
Ile	His	Arg	Leu	Lys	Pro	Ser	Asp	Ala	Gly	Val	Tyr	Thr	Cys	Ser	Ala
225					230					235					240
Gly	Pro	Ala	Arg	Glu	His	Phe	Val	Ile	Lys	Leu	Ile	Gly	Gly	Asn	Arg
				245					250					255	
Lys	Leu	Val	Ala	Arg	Pro	Leu	Ser	Pro	Arg	Ser	Glu	Glu	Glu	Val	Leu
			260				265						270		
Ala	Gly	Arg	Lys	Gly	Gly	Pro	Lys	Glu	Ala	Leu	Gln	Thr	His	Lys	His
		275					280					285			
Gln	Asn	Gly	Ile	Phe	Ser	Asn	Gly	Ser	Lys	Ala	Glu	Lys	Arg	Gly	Leu
	290					295					300				
Ala	Ala	Asn	Pro	Gly	Ser	Arg	Tyr	Asp	Asp	Leu	Val	Ser	Arg	Leu	Leu
305					310					315					320
Glu	Gln	Gly	Gly	Trp	Pro	Gly	Glu	Leu	Leu	Ala	Ser	Trp	Glu	Ala	Gln
				325				330						335	
Asp	Ser	Ala	Glu	Arg	Asn	Thr	Thr	Ser	Glu	Glu	Asp	Pro	Gly	Ala	Glu
			340					345					350		
Gln	Val	Leu	Leu	His	Leu	Pro	Phe	Thr	Met	Val	Thr	Glu	Gln	Arg	Arg
		355					360					365			
Leu	Asp	Asp	Ile	Leu	Gly	Asn	Leu	Ser	Gln	Gln	Pro	Glu	Glu	Leu	Arg
	370					375					380				
Asp	Leu	Tyr	Ser	Lys	His	Leu	Val	Ala	Gln	Leu	Ala	Gln	Glu	Ile	Phe

90

385 390 395 400
 Arg Ser His Leu Glu His Gln Asp Thr Leu Leu Lys Pro Ser Glu Arg
 405 410 415
 Arg Thr Ser Pro Val Thr Leu Ser Pro His Lys His Val Ser Gly Phe
 420 425 430
 Ser Ser Ser Leu Arg Thr Ser Ser Thr Gly Asp Ala Gly Gly Gly Ser
 435 440 445
 Arg Arg Pro His Arg Lys Pro Thr Ile Leu Arg Lys Ile Ser Ala Ala
 450 455 460
 Gln Gln Leu Ser Ala Ser Glu Val Val Thr His Leu Gly Gln Thr Val
 465 470 475 480
 Ala Leu Ala Ser Gly Thr Leu Ser Val Phe Cys Thr Val Arg Pro Ser
 485 490 495
 Ala Thr Gln Gly Leu Pro Ser Ala Gly Pro Gly Met Glu Lys Lys Ser
 500 505 510
 Val Gln

<210> 125
 <211> 262
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (254)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 125
 Met Glu Cys Cys Arg Arg Ala Thr Pro Gly Thr Leu Leu Leu Phe Leu
 1 5 10 15
 Ala Phe Leu Leu Leu Ser Ser Arg Thr Ala Arg Ser Glu Glu Asp Arg
 20 25 30
 Asp Gly Leu Trp Asp Ala Trp Gly Pro Trp Ser Glu Cys Ser Arg Thr
 35 40 45
 Cys Gly Gly Gly Ala Ser Tyr Ser Leu Arg Arg Cys Leu Ser Ser Lys
 50 55 60
 Ser Cys Glu Gly Arg Asn Ile Arg Tyr Arg Thr Cys Ser Asn Val Asp
 65 70 75 80
 Cys Pro Pro Glu Ala Gly Asp Phe Arg Ala Gln Gln Cys Ser Ala His
 85 90 95
 Asn Asp Val Lys His His Gly Gln Phe Tyr Glu Trp Leu Pro Val Ser
 100 105 110
 Asn Asp Pro Asp Asn Pro Cys Ser Leu Lys Cys Gln Ala Lys Gly Thr
 115 120 125
 Thr Leu Val Val Glu Leu Ala Pro Lys Val Leu Asp Gly Thr Arg Cys
 130 135 140
 Tyr Thr Glu Ser Leu Asp Met Cys Ile Ser Gly Leu Cys Gln Ile Val

91

145 150 155 160
 Gly Cys Asp His Gln Leu Gly Ser Thr Val Lys Glu Asp Asn Cys Gly
 165 170 175
 Val Cys Asn Gly Asp Gly Ser Thr Cys Arg Leu Val Arg Gly Gln Tyr
 180 185 190
 Lys Ser Gln Leu Ser Ala Thr Lys Ser Asp Asp Thr Val Val Ala Ile
 195 200 205
 Pro Tyr Gly Ser Arg His Ile Arg Leu Val Leu Lys Gly Pro Asp His
 210 215 220
 Leu Tyr Leu Glu Thr Lys Thr Leu Gln Gly Thr Lys Gly Glu Asn Ser
 225 230 235 240
 Leu Ser Ser Thr Gly Thr Phe Leu Val Asp Asn Ser Ser Xaa Thr Ser
 245 250 255
 Arg Asn Phe Gln Thr Lys
 260

<210> 126
 <211> 115
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (101)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (106)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 126
 Ile Ser Leu Leu Trp Asn Leu Trp Gln Ser Val Lys Ile Gly Cys Gly
 1 5 10 15
 Glu Lys Leu Tyr Pro Gly His Thr Lys Asp Ser Arg Asn His Leu Gly
 20 25 30
 Gln Asn Leu Ser Phe Leu His Phe Ile Tyr Leu Phe Pro Pro Pro His
 35 40 45
 Ser Thr His Thr Leu Pro Thr Ser Ser Thr Ser Thr Phe Lys His Lys
 50 55 60
 Asp Val Arg Val Phe Ser Leu Ser Val Ser Trp Arg Thr Gly Cys Trp
 65 70 75 80
 Glu Arg Lys Gly Gln Met Ser Lys Gly Gly Cys Arg Ala Gly Gln Ala
 85 90 95
 Asp Ser Gly Gly Xaa Leu Glu Glu Leu Xaa Pro Ser Gln Thr Trp Val
 100 105 110
 Ser Lys Thr
 115

<210> 127

<211> 350
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (3)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (4)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 127
 Met Ala Xaa Xaa Val Val Leu Leu Ala Leu Val Ala Gly Val Leu Gly
 1 5 10 15
 Asn Glu Phe Ser Ile Leu Lys Ser Pro Gly Ser Val Val Phe Arg Asn
 20 25 30
 Gly Asn Trp Pro Ile Pro Gly Glu Arg Ile Pro Asp Val Ala Ala Leu
 35 40 45
 Ser Met Gly Phe Ser Val Lys Glu Asp Leu Ser Trp Pro Gly Leu Ala
 50 55 60
 Val Gly Asn Leu Phe His Arg Pro Arg Ala Thr Val Met Val Met Val
 65 70 75 80
 Lys Gly Val Asn Lys Leu Ala Leu Pro Pro Gly Ser Val Ile Ser Tyr
 85 90 95
 Pro Leu Glu Asn Ala Val Pro Phe Ser Leu Asp Ser Val Ala Asn Ser
 100 105 110
 Ile His Ser Leu Phe Ser Glu Glu Thr Pro Val Val Leu Gln Leu Ala
 115 120 125
 Pro Ser Glu Glu Arg Val Tyr Met Val Gly Lys Ala Asn Ser Val Phe
 130 135 140
 Glu Asp Leu Ser Val Thr Leu Arg Gln Leu Arg Asn Arg Leu Phe Gln
 145 150 155 160
 Glu Asn Ser Val Leu Ser Ser Leu Pro Leu Asn Ser Leu Ser Arg Asn
 165 170 175
 Asn Glu Val Asp Leu Leu Phe Leu Ser Glu Leu Gln Val Leu His Asp
 180 185 190
 Ile Ser Ser Leu Leu Ser Arg His Lys His Leu Ala Lys Asp His Ser
 195 200 205
 Pro Asp Leu Tyr Ser Leu Glu Leu Ala Gly Leu Asp Glu Ile Gly Lys
 210 215 220
 Arg Tyr Gly Glu Asp Ser Glu Gln Phe Arg Asp Ala Ser Lys Ile Leu
 225 230 235 240
 Val Asp Ala Leu Gln Lys Phe Ala Asp Asp Met Tyr Ser Leu Tyr Gly
 245 250 255
 Gly Asn Ala Val Val Glu Leu Val Thr Val Lys Ser Phe Asp Thr Ser
 260 265 270

Leu	Ile	Arg 275	Lys	Thr	Arg	Thr	Ile 280	Leu	Glu	Ala	Lys	Gln 285	Ala	Lys	Asn
Pro	Ala 290	Ser	Pro	Tyr	Asn	Leu 295	Ala	Tyr	Lys	Tyr	Asn 300	Phe	Glu	Tyr	Ser
Val 305	Val	Phe	Asn	Met	Val 310	Leu	Trp	Ile	Met	Ile 315	Ala	Leu	Ala	Leu	Ala 320
Val	Ile	Ile	Thr	Ser 325	Tyr	Asn	Ile	Trp	Asn 330	Met	Asp	Pro	Gly	Tyr 335	Asp
Ser	Ile	Ile	Tyr 340	Arg	Met	Thr	Asn 345	Gln	Lys	Ile	Arg	Met	Asp 350		

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<210> 128
<211> 339
<212> PRT
<213> Homo sapiens
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<400> 128																
Met 1	Ser	Trp	Ser	Thr 5	Phe	Leu	Leu	Ala	Glu 10	Ala	Cys	Gly	Phe	Thr 15	Gly	
Val	Val	Ala	Val 20	Leu	Phe	Cys	Gly	Ile 25	Thr	Gln	Ala	His	Tyr 30	Thr	Tyr	
Asn	Asn	Leu 35	Ser	Val	Glu	Ser	Arg 40	Ser	Arg	Thr	Lys	Gln 45	Leu	Phe	Glu	
Val	Leu 50	His	Phe	Leu	Ala	Glu 55	Asn	Phe	Ile	Phe	Ser 60	Tyr	Met	Gly	Leu	
Ala 65	Leu	Phe	Thr	Phe	Gln 70	Lys	His	Val	Phe	Ser 75	Pro	Ile	Phe	Ile	Ile 80	
Gly	Ala	Phe	Val	Ala 85	Ile	Phe	Leu	Gly	Arg 90	Ala	Ala	His	Ile	Tyr 95	Pro	
Leu	Ser	Phe	Phe 100	Leu	Asn	Leu	Gly	Arg 105	Arg	His	Lys	Ile	Gly 110	Trp	Asn	
Phe	Gln	His 115	Met	Met	Met	Phe	Ser 120	Gly	Leu	Arg	Gly	Ala 125	Met	Ala	Phe	
Ala 130	Leu	Ala	Ile	Arg	Asp	Thr 135	Ala	Ser	Tyr	Ala	Arg 140	Gln	Met	Met	Phe	
Thr 145	Thr	Thr	Leu	Leu	Ile 150	Val	Phe	Phe	Thr	Val 155	Trp	Ile	Ile	Gly	Gly 160	
Gly	Thr	Thr	Pro	Met 165	Leu	Ser	Trp	Leu	Asn 170	Ile	Arg	Val	Gly 175	Val	Asp	
Pro	Asp	Gln	Asp 180	Pro	Pro	Pro	Asn	Asn 185	Asp	Ser	Phe	Gln	Val 190	Leu	Gln	
Gly	Asp	Gly 195	Pro	Asp	Ser	Ala	Arg 200	Gly	Asn	Arg	Thr	Lys 205	Gln	Glu	Ser	
Ala 210	Trp	Ile	Phe	Arg	Leu	Trp 215	Tyr	Ser	Phe	Asp	His 220	Asn	Tyr	Leu	Lys	
Pro 225	Ile	Leu	Thr	His	Ser 230	Gly	Pro	Pro	Leu	Thr 235	Thr	Thr	Leu	Pro	Ala 240	

Trp	Cys	Gly	Leu	Leu	Ala	Arg	Cys	Leu	Thr	Ser	Pro	Gln	Val	Tyr	Asp
				245					250					255	
Asn	Gln	Glu	Pro	Leu	Arg	Glu	Glu	Asp	Ser	Asp	Phe	Ile	Leu	Thr	Glu
			260					265					270		
Gly	Asp	Leu	Thr	Leu	Thr	Tyr	Gly	Asp	Ser	Thr	Val	Thr	Ala	Asn	Gly
		275					280					285			
Ser	Ser	Ser	Ser	His	Thr	Ala	Ser	Thr	Ser	Leu	Glu	Gly	Ser	Arg	Arg
	290					295					300				
Thr	Lys	Ser	Ser	Ser	Glu	Glu	Val	Leu	Glu	Arg	Asp	Leu	Gly	Met	Gly
305					310					315					320
Asp	Gln	Lys	Val	Ser	Ser	Arg	Gly	Thr	Arg	Leu	Val	Phe	Pro	Leu	Glu
				325					330					335	

Asp Asn Ala

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<210> 129
<211> 339
<212> PRT
<213> Homo sapiens
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<400> 129																
Met	Ser	Trp	Ser	Thr	Phe	Leu	Leu	Ala	Glu	Ala	Cys	Gly	Phe	Thr	Gly	
1				5					10					15		
Val	Val	Ala	Val	Leu	Phe	Cys	Gly	Ile	Thr	Gln	Ala	His	Tyr	Thr	Tyr	
			20					25					30			
Asn	Asn	Leu	Ser	Val	Glu	Ser	Arg	Ser	Arg	Thr	Lys	Gln	Leu	Phe	Glu	
		35					40					45				
Val	Leu	His	Phe	Leu	Ala	Glu	Asn	Phe	Ile	Phe	Ser	Tyr	Met	Gly	Leu	
	50					55					60					
Ala	Leu	Phe	Thr	Phe	Gln	Lys	His	Val	Phe	Ser	Pro	Ile	Phe	Ile	Ile	
65					70					75					80	
Gly	Ala	Phe	Val	Ala	Ile	Phe	Leu	Gly	Arg	Ala	Ala	His	Ile	Tyr	Pro	
				85					90					95		
Leu	Ser	Phe	Phe	Leu	Asn	Leu	Gly	Arg	Arg	His	Lys	Ile	Gly	Trp	Asn	
			100					105					110			
Phe	Gln	His	Met	Met	Met	Phe	Ser	Gly	Leu	Arg	Gly	Ala	Met	Ala	Phe	
		115					120					125				
Ala	Leu	Ala	Ile	Arg	Asp	Thr	Ala	Ser	Tyr	Ala	Arg	Gln	Met	Met	Phe	
	130					135					140					
Thr	Thr	Thr	Leu	Leu	Ile	Val	Phe	Phe	Thr	Val	Trp	Ile	Ile	Gly	Gly	
145					150					155					160	
Gly	Thr	Thr	Pro	Met	Leu	Ser	Trp	Leu	Asn	Ile	Arg	Val	Gly	Val	Asp	
				165					170					175		
Pro	Asp	Gln	Asp	Pro	Pro	Pro	Asn	Asn	Asp	Ser	Phe	Gln	Val	Leu	Gln	
			180					185					190			
Gly	Asp	Gly	Pro	Asp	Ser	Ala	Arg	Gly	Asn	Arg	Thr	Lys	Gln	Glu	Ser	

195					200					205					
Ala	Trp	Ile	Phe	Arg	Leu	Trp	Tyr	Ser	Phe	Asp	His	Asn	Tyr	Leu	Lys
210						215					220				
Pro	Ile	Leu	Thr	His	Ser	Gly	Pro	Pro	Leu	Thr	Thr	Thr	Leu	Pro	Ala
225					230					235					240
Trp	Cys	Gly	Leu	Leu	Ala	Arg	Cys	Leu	Thr	Ser	Pro	Gln	Val	Tyr	Asp
				245					250					255	
Asn	Gln	Glu	Pro	Leu	Arg	Glu	Glu	Asp	Ser	Asp	Phe	Ile	Leu	Thr	Glu
			260					265					270		
Gly	Asp	Leu	Thr	Leu	Thr	Tyr	Gly	Asp	Ser	Thr	Val	Thr	Ala	Asn	Gly
		275					280					285			
Ser	Ser	Ser	Ser	His	Thr	Ala	Ser	Thr	Ser	Leu	Glu	Gly	Ser	Arg	Arg
	290					295					300				
Thr	Lys	Ser	Ser	Ser	Glu	Glu	Val	Leu	Glu	Arg	Asp	Leu	Gly	Met	Gly
305					310					315					320
Asp	Gln	Lys	Val	Ser	Ser	Arg	Gly	Thr	Arg	Leu	Val	Phe	Pro	Leu	Glu
				325					330					335	

Asp Asn Ala

<210> 130
 <211> 472
 <212> PRT
 <213> Homo sapiens

<400> 130
 Met Ile Arg Thr Arg Arg Gly Trp Ser Ser Met Trp Pro Trp Ile Gly
 1 5 10 15
 Val Gly Tyr Leu Ala Gly Cys Leu Val His Ala Leu Gly Glu Lys Gln
 20 25 30
 Pro Glu Leu Gln Ile Ser Glu Arg Asp Val Leu Cys Val Gln Ile Ala
 35 40 45
 Gly Leu Cys His Asp Leu Gly His Gly Pro Phe Ser His Met Phe Asp
 50 55 60
 Gly Arg Phe Ile Pro Leu Ala Arg Pro Glu Val Lys Trp Thr His Glu
 65 70 75 80
 Gln Gly Ser Val Met Met Phe Glu His Leu Ile Asn Ser Asn Gly Ile
 85 90 95
 Lys Pro Val Met Glu Gln Tyr Gly Leu Ile Pro Glu Glu Asp Ile Cys
 100 105 110
 Phe Ile Lys Glu Gln Ile Val Gly Pro Leu Glu Ser Pro Val Glu Asp
 115 120 125
 Ser Leu Trp Pro Tyr Lys Gly Arg Pro Glu Asn Lys Ser Phe Leu Tyr
 130 135 140
 Glu Ile Val Ser Asn Lys Arg Asn Gly Ile Asp Val Asp Lys Trp Asp
 145 150 155 160

Tyr Phe Ala Arg Asp Cys His His Leu Gly Ile Gln Asn Asn Phe Asp
 165 170 175
 Tyr Lys Arg Phe Ile Lys Phe Ala Arg Val Cys Glu Val Asp Asn Glu
 180 185 190
 Leu Arg Ile Cys Ala Arg Asp Lys Glu Val Gly Asn Leu Tyr Asp Met
 195 200 205
 Phe His Thr Arg Asn Ser Leu His Arg Arg Ala Tyr Gln His Lys Val
 210 215 220
 Gly Asn Ile Ile Asp Thr Met Ile Thr Asp Ala Phe Leu Glu Ala Asp
 225 230 235 240
 Asp Tyr Ile Glu Ile Thr Gly Ala Gly Gly Lys Lys Tyr Arg Ile Ser
 245 250 255
 Thr Ala Ile Asp Asp Met Glu Ala Tyr Thr Lys Leu Thr Asp Asn Ile
 260 265 270
 Phe Leu Glu Ile Leu Tyr Ser Thr Asp Pro Lys Leu Lys Asp Ala Arg
 275 280 285
 Glu Ile Leu Lys Gln Ile Glu Tyr Arg Asn Leu Phe Lys Tyr Val Gly
 290 295 300
 Glu Thr Gln Pro Thr Gly Gln Ile Lys Ile Lys Arg Glu Asp Tyr Glu
 305 310 315 320
 Ser Leu Pro Lys Glu Val Ala Ser Ala Lys Pro Lys Val Leu Leu Asp
 325 330 335
 Val Lys Leu Lys Ala Glu Asp Phe Ile Val Asp Val Ile Asn Met Asp
 340 345 350
 Tyr Gly Met Gln Glu Lys Asn Pro Ile Asp His Val Ser Phe Tyr Cys
 355 360 365
 Lys Thr Ala Pro Asn Arg Ala Ile Arg Ile Thr Lys Asn Gln Val Ser
 370 375 380
 Gln Leu Leu Pro Glu Lys Phe Ala Glu Gln Leu Ile Arg Val Tyr Cys
 385 390 395 400
 Lys Lys Val Asp Arg Lys Ser Leu Tyr Ala Ala Arg Gln Tyr Phe Val
 405 410 415
 Gln Trp Cys Ala Asp Arg Asn Phe Thr Lys Pro Gln Asp Gly Asp Val
 420 425 430
 Ile Ala Pro Leu Ile Thr Pro Gln Lys Lys Glu Trp Asn Asp Ser Thr
 435 440 445
 Ser Val Gln Asn Pro Thr Arg Leu Arg Glu Ala Ser Lys Ser Arg Val
 450 455 460
 Gln Leu Phe Lys Asp Asp Pro Met
 465 470

<210> 131

<211> 42

<212> PRT

<213> Homo sapiens

97

<400> 131

Met Glu Cys Lys Lys Arg Ile Gln Leu Ile Met Leu Ala Ser Ile Val
 1 5 10 15

Arg Leu Pro Pro Thr Glu Gln Ser Gly Leu Leu Lys Thr Arg Phe His
 20 25 30

Asn Phe Cys Gln Arg Asn Leu Gln Ser Ser
 35 40

<210> 132

<211> 122

<212> PRT

<213> Homo sapiens

<400> 132

Met Trp Gly Trp Gly Ser Leu Val Ser Ala Arg Gly Gly Trp Gly Val
 1 5 10 15

Phe Ile Tyr Leu Tyr Met Gly Leu Tyr Ile Val Leu Trp Gly Met Gly
 20 25 30

Glu Pro Ala Gly Gly Glu Asn Pro Pro Leu Ser Pro His Pro Pro Gly
 35 40 45

Arg Ala Asn Val Lys Leu Leu Ile Phe Val Leu Tyr Ile Phe Tyr Ile
 50 55 60

Asn Ile Ser Ile Phe Phe Leu Gln Asn Gln Phe Ile Asn Gly Arg Gly
 65 70 75 80

Val Trp Gly Gly His Met Glu Leu Pro Leu Trp Gly Gly Pro Leu His
 85 90 95

Tyr Pro Thr Tyr Arg Pro Phe Pro His Pro Pro Pro His Ser Pro Pro
 100 105 110

Pro Gly Cys Asp Cys Cys Lys Met Gly Val
 115 120

<210> 133

<211> 252

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (86)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (116)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (135)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (146)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 133

Met Ala Val Gly Lys Phe Leu Leu Gly Ser Leu Leu Leu Leu Ser Leu
 1 5 10 15

Gln Leu Gly Gln Gly Trp Gly Pro Asp Ala Arg Gly Val Pro Val Ala
 20 25 30

Asp Gly Glu Phe Ser Ser Glu Gln Val Ala Lys Ala Gly Gly Thr Trp
 35 40 45

Leu Gly Lys Asp Phe Gln Gly Pro Ser Val Thr Ser Gln Leu Ser Pro
 50 55 60

Ala Leu Thr Leu Leu Thr Val Ser Ala Leu Pro Ser His Arg His Pro
 65 70 75 80

Pro Pro Pro Cys Pro Xaa Ala Pro Ser Pro Val Trp Ser Met Pro Ala
 85 90 95

Val Glu Pro Asp Pro Val Arg Gly Arg Ala Arg Pro Gly Leu Arg Leu
 100 105 110

Ile Gly Glu Xaa His Leu Pro Leu Leu Arg Arg Gln Leu Pro Pro Trp
 115 120 125

Cys Pro His Pro Ala Trp Xaa Gly Ala Gly Pro Ala Ala Gly Pro Gly
 130 135 140

Pro Xaa Pro Arg Arg Ala Leu Leu Pro Ala His Ser Leu His Arg Arg
 145 150 155 160

Gly Leu Pro Arg Arg Pro Pro Arg Trp Gln Arg Leu Pro Gln Leu Ser
 165 170 175

Ala Ala Leu Arg Leu Trp Trp Leu Arg Val Pro Gly Leu Ala Pro Arg
 180 185 190

Ser Cys Ser Ala Gly Gly Ala Arg Leu Thr Tyr Leu Leu Glu Thr Trp
 195 200 205

Met Gln Arg Gln Arg Gly Gly Glu Trp Ala Gly Ala Thr Ser Ser Glu
 210 215 220

Cys Asn Lys Gly His His Ser Pro Gly Lys Lys Lys Lys Lys Lys Lys
 225 230 235 240

Lys Lys Lys Lys Lys Leu Glu Gly Gly Ser Arg Tyr
 245 250

<210> 134

<211> 132

<212> PRT

<213> Homo sapiens

<400> 134

Met Thr Leu Phe Gly Leu Phe Val Ser Leu Val Phe Leu Gly Gln Ala
 1 5 10 15

Phe Thr Ile Met Leu Val Tyr Val Trp Ser Arg Arg Asn Pro Tyr Val
 20 25 30

Arg Met Asn Phe Phe Gly Leu Leu Asn Phe Gln Ala Pro Phe Leu Pro
 35 40 45

Trp Val Leu Met Gly Phe Ser Leu Leu Leu Gly Asn Ser Ile Ile Val
 50 55 60
 Asp Leu Leu Gly Ile Ala Val Gly His Ile Tyr Phe Phe Leu Glu Asp
 65 70 75 80
 Val Phe Pro Asn Gln Pro Gly Gly Ile Arg Ile Leu Lys Thr Pro Ser
 85 90 95
 Ile Leu Lys Ala Ile Phe Asp Thr Pro Asp Glu Asp Pro Asn Tyr Asn
 100 105 110
 Pro Leu Pro Glu Glu Arg Pro Gly Gly Phe Ala Trp Gly Glu Gly Gln
 115 120 125
 Arg Leu Gly Gly
 130

<210> 135
 <211> 156
 <212> PRT
 <213> Homo sapiens

<400> 135
 Met Leu Glu Glu Gly Ser Phe Arg Gly Arg Thr Ala Asp Phe Val Phe
 1 5 10 15
 Met Phe Leu Phe Gly Gly Phe Leu Met Thr Leu Phe Gly Leu Phe Val
 20 25 30
 Ser Leu Val Phe Leu Gly Gln Ala Phe Thr Ile Met Leu Val Tyr Val
 35 40 45
 Trp Ser Arg Arg Asn Pro Tyr Val Arg Met Asn Phe Phe Gly Leu Leu
 50 55 60
 Asn Phe Gln Ala Pro Phe Leu Pro Trp Val Leu Met Gly Phe Ser Leu
 65 70 75 80
 Leu Leu Gly Asn Ser Ile Ile Val Asp Leu Leu Gly Ile Ala Val Gly
 85 90 95
 His Ile Tyr Phe Phe Leu Glu Asp Val Phe Pro Asn Gln Pro Gly Gly
 100 105 110
 Ile Arg Ile Leu Lys Thr Pro Ser Ile Leu Lys Ala Ile Phe Asp Thr
 115 120 125
 Pro Asp Glu Asp Pro Asn Tyr Asn Pro Leu Pro Glu Glu Arg Pro Gly
 130 135 140
 Gly Phe Ala Trp Gly Glu Gly Gln Arg Leu Gly Gly
 145 150 155

<210> 136
 <211> 140
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (36)
 <223> Xaa equals any of the naturally occurring L-amino acids

100

<400> 136

Met Phe Leu Phe Gly Gly Phe Leu Met Thr Leu Phe Gly Leu Phe Val
 1 5 10 15
 Ser Leu Val Phe Leu Gly Gln Ala Phe Thr Ile Met Leu Val Tyr Val
 20 25 30
 Trp Ser Arg Xaa Asn Pro Tyr Val Arg Met Asn Phe Phe Gly Leu Leu
 35 40 45
 Asn Phe Gln Ala Pro Phe Leu Pro Trp Val Leu Met Gly Phe Ser Leu
 50 55 60
 Leu Leu Gly Asn Ser Ile Ile Val Asp Leu Leu Gly Ile Ala Val Gly
 65 70 75 80
 His Ile Tyr Phe Phe Leu Glu Asp Val Phe Pro Asn Gln Pro Gly Gly
 85 90 95
 Ile Arg Ile Leu Lys Thr Pro Ser Ile Leu Lys Ala Ile Phe Asp Thr
 100 105 110
 Pro Asp Glu Asp Pro Asn Tyr Asn Pro Leu Pro Glu Glu Arg Pro Gly
 115 120 125
 Gly Phe Ala Trp Gly Glu Gly Gln Arg Leu Gly Gly
 130 135 140

<210> 137

<211> 50

<212> PRT

<213> Homo sapiens

<400> 137

Met Gln Val Lys Asn Ser Ile His Val Thr Phe Val Ala Arg Ile Leu
 1 5 10 15
 Val Arg Val Leu Ile Cys Leu Ser Thr Ser Glu Ala Ile Leu Ala Arg
 20 25 30
 Asn His Ile Tyr Val Val Ser Val Thr Asn Ala Ser Val Glu Val Gln
 35 40 45
 Thr Ser
 50

<210> 138

<211> 172

<212> PRT

<213> Homo sapiens

<400> 138

Gly Thr Arg Thr Glu Arg Asp Glu Leu Leu Lys Asp Leu Gln Gln Ser
 1 5 10 15
 Ile Ala Arg Glu Pro Ser Ala Pro Ser Ile Pro Thr Pro Ala Tyr Gln
 20 25 30
 Ser Leu Pro Ala Gly Gly His Ala Pro Thr Pro Pro Thr Pro Ala Pro
 35 40 45
 Arg Thr Met Pro Pro Thr Lys Pro Gln Pro Pro Ala Arg Pro Pro Pro
 50 55 60

101

Pro Val Leu Pro Ala Asn Arg Ala Pro Ser Ala Thr Ala Pro Ser Pro
 65 70 75 80
 Val Gly Ala Gly Thr Ala Ala Pro Ala Pro Ser Gln Thr Pro Gly Ser
 85 90 95
 Ala Pro Pro Pro Gln Ala Gln Gly Pro Pro Tyr Pro Thr Tyr Pro Gly
 100 105 110
 Tyr Pro Gly Tyr Cys Gln Met Pro Met Pro Met Gly Tyr Asn Pro Tyr
 115 120 125
 Ala Tyr Gly Gln Tyr Asn Met Pro Tyr Pro Pro Val Tyr His Gln Ser
 130 135 140
 Pro Gly Gln Ala Pro Tyr Pro Gly Pro Gln Gln Pro Ser Tyr Pro Phe
 145 150 155 160
 Pro Gln Pro Pro Gln Gln Ser Tyr Tyr Pro Gln Gln
 165 170

<210> 139
 <211> 142
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (111)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 139
 Met His Gln Leu Leu Gln Leu Gln Arg Gln Glu Pro Cys Arg Leu Leu
 1 5 10 15
 Ser Pro Ser Pro Gln Pro Gly Leu His His Leu Cys Phe Gln Gln Ile
 20 25 30
 Glu Leu Leu Leu Leu Leu Leu His Leu Gln Trp Gly Leu Gly Leu Leu
 35 40 45
 Arg Gln Leu His His Lys Arg Leu Ala Gln Leu Leu Leu His Arg Arg
 50 55 60
 Arg Asp His Pro Ile Pro Pro Ile Gln Asp Ile Leu Gly Ile Ala Lys
 65 70 75 80
 Cys Pro Cys Pro Trp Ala Ile Ile Leu Met Arg Met Ala Ser Ile Ile
 85 90 95
 Cys His Ile His Gln Cys Ile Thr Arg Val Leu Asp Arg Leu Xaa Thr
 100 105 110
 Arg Asp Pro Ser Ser Leu His Thr Pro Ser Leu Ser Pro His Ser Ser
 115 120 125
 Leu Thr Ile His Ser Ser Asn Met Ser Ala Gln Gln Leu Ser
 130 135 140

<210> 140
 <211> 193
 <212> PRT
 <213> Homo sapiens

102

<400> 140

Met Glu Pro Gly Pro Thr Ala Ala Gln Arg Arg Cys Ser Leu Pro Pro
 1 5 10 15
 Trp Leu Pro Leu Gly Leu Leu Leu Trp Ser Gly Leu Ala Leu Gly Ala
 20 25 30
 Leu Pro Phe Gly Ser Ser Pro His Arg Val Phe His Asp Leu Leu Ser
 35 40 45
 Glu Gln Gln Leu Leu Glu Val Glu Asp Leu Ser Leu Ser Leu Leu Gln
 50 55 60
 Gly Gly Gly Leu Gly Pro Leu Ser Leu Pro Pro Asp Leu Pro Asp Leu
 65 70 75 80
 Asp Pro Glu Cys Arg Glu Leu Leu Leu Asp Phe Ala Asn Ser Ser Ala
 85 90 95
 Glu Leu Thr Gly Cys Leu Val Arg Ser Ala Arg Pro Val Arg Leu Cys
 100 105 110
 Gln Thr Cys Tyr Pro Leu Phe Gln Gln Val Val Ser Lys Met Asp Asn
 115 120 125
 Ile Ser Arg Ala Ala Gly Asn Thr Ser Glu Ser Gln Ser Cys Ala Arg
 130 135 140
 Ser Leu Leu Met Ala Asp Arg Met Gln Ile Val Val Ile Leu Ser Glu
 145 150 155 160
 Phe Phe Asn Thr Thr Trp Gln Glu Ala Asn Cys Ala Asn Cys Leu Thr
 165 170 175
 Asn Asn Ser Glu Glu Leu Ser Asn Ser Thr Val Tyr Phe Leu Lys Ser
 180 185 190
 Ile

<210> 141

<211> 134

<212> PRT

<213> Homo sapiens

<400> 141

Met Ala Pro Glu Val Met Glu Gln Val Arg Gly Tyr Asp Phe Lys Ala
 1 5 10 15
 Asp Ile Trp Ser Phe Gly Ile Thr Ala Ile Glu Leu Ala Thr Gly Ala
 20 25 30
 Ala Pro Tyr His Lys Tyr Pro Pro Met Lys Val Leu Met Leu Thr Leu
 35 40 45
 Gln Asn Asp Pro Pro Ser Leu Glu Thr Gly Val Gln Asp Lys Glu Met
 50 55 60
 Leu Lys Lys Tyr Gly Lys Ser Phe Arg Lys Met Ile Ser Leu Cys Leu
 65 70 75 80
 Gln Lys Asp Pro Glu Lys Arg Pro Thr Ala Ala Glu Leu Leu Arg His
 85 90 95
 Lys Phe Phe Gln Lys Ala Lys Asn Lys Glu Phe Leu Gln Glu Lys Thr

103

100	105	110
Leu Gln Arg Ala Pro Thr Ile Ser Glu Arg Ala Lys Lys Val Arg Arg		
115	120	125
Val Pro Gly Ser Cys Pro		
130		

<210> 142
 <211> 73
 <212> PRT
 <213> Homo sapiens

<400> 142
 Met Asn Ile Thr Arg Lys Leu Trp Ser Arg Thr Phe Asn Cys Ser Val
 1 5 10 15
 Pro Cys Ser Asp Thr Val Pro Val Ile Ala Val Ser Val Phe Ile Leu
 20 25 30
 Phe Leu Pro Val Val Phe Tyr Leu Ser Ser Phe Leu His Ser Glu Gln
 35 40 45
 Lys Lys Arg Lys Leu Ile Leu Pro Lys Arg Leu Lys Ser Ser Thr Ser
 50 55 60
 Phe Ala Asn Ile Gln Glu Asn Ser Asn
 65 70

<210> 143
 <211> 144
 <212> PRT
 <213> Homo sapiens

<400> 143
 Met Pro Thr Thr Thr Glu Gln Pro Val Thr Thr Thr Phe Pro Val Thr
 1 5 10 15
 Thr Gly Leu Lys Pro Thr Val Ala Leu Cys Gln Gln Lys Cys Arg Arg
 20 25 30
 Thr Gly Thr Leu Glu Gly Asn Tyr Cys Ser Ser Asp Phe Val Leu Ala
 35 40 45
 Gly Thr Val Ile Thr Thr Ile Thr Arg Asp Gly Ser Leu His Ala Thr
 50 55 60
 Val Ser Ile Ile Asn Ile Tyr Lys Glu Gly Asn Leu Ala Ile Gln Gln
 65 70 75 80
 Ala Gly Lys Asn Met Ser Ala Arg Leu Thr Val Val Cys Lys Gln Cys
 85 90 95
 Pro Leu Leu Arg Arg Gly Leu Asn Tyr Ile Ile Met Gly Gln Val Gly
 100 105 110
 Glu Asp Gly Arg Gly Lys Ile Met Pro Asn Ser Phe Ile Met Met Phe
 115 120 125
 Lys Thr Lys Asn Gln Lys Leu Leu Asp Ala Leu Lys Asn Lys Gln Cys
 130 135 140

<210> 144
 <211> 189
 <212> PRT
 <213> Homo sapiens

<400> 144
 Met Gly Gly Gln Val Ala Gly Val Tyr Ala Ala Tyr Tyr Pro Ser Asp
 1 5 10 15
 Val Ser Ser Leu Cys Leu Val Cys Pro Ala Gly Leu Gln Tyr Ser Thr
 20 25 30
 Asp Asn Gln Phe Val Gln Arg Leu Lys Glu Leu Gln Gly Ser Ala Ala
 35 40 45
 Val Glu Lys Ile Pro Leu Ile Pro Ser Thr Pro Glu Glu Met Ser Glu
 50 55 60
 Met Leu Gln Leu Cys Ser Tyr Val Arg Phe Lys Val Pro Gln Gln Ile
 65 70 75 80
 Leu Gln Gly Leu Val Asp Val Arg Ile Pro His Asn Asn Phe Tyr Arg
 85 90 95
 Lys Leu Phe Leu Glu Ile Val Ser Glu Lys Ser Arg Tyr Ser Leu His
 100 105 110
 Gln Asn Met Asp Lys Ile Lys Val Pro Thr Gln Ile Ile Trp Gly Lys
 115 120 125
 Gln Asp Gln Val Leu Asp Val Ser Gly Ala Asp Met Leu Ala Lys Ser
 130 135 140
 Ile Ala Asn Cys Gln Val Glu Leu Leu Glu Asn Cys Gly His Ser Val
 145 150 155 160
 Val Met Glu Arg Pro Arg Lys Thr Ala Lys Leu Ile Ile Asp Phe Leu
 165 170 175
 Ala Ser Val His Asn Thr Asp Asn Asn Lys Lys Leu Asp
 180 185

<210> 145
 <211> 487
 <212> PRT
 <213> Homo sapiens

<400> 145
 Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
 1 5 10 15
 Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
 20 25 30
 Pro Ser Glu Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
 35 40 45
 Ser Ser Gly Gly His Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys
 50 55 60
 Gly Leu Glu Trp Ile Gly Tyr Ile Ser Tyr Asn Gly Val Thr Tyr Tyr
 65 70 75 80

105

Asn	Pro	Ser	Leu	Lys	Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Thr	Ser	Gln	85	90	95
Asn	Gln	Phe	Ser	Leu	Arg	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala	100	105	110
Val	Tyr	Tyr	Cys	Ala	Lys	Asp	His	Arg	Ala	Thr	Arg	Asp	Gly	Tyr	Gln	115	120	125
Leu	Glu	Tyr	Arg	Gly	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	Ile	Leu	Val	Thr	130	135	140
Val	Ser	Ser	Ala	Ser	Pro	Thr	Ser	Pro	Lys	Val	Phe	Pro	Leu	Ser	Leu	145	150	155
Asp	Ser	Thr	Pro	Gln	Asp	Gly	Asn	Val	Val	Val	Ala	Cys	Leu	Val	Gln	165	170	175
Gly	Phe	Phe	Pro	Gln	Glu	Pro	Leu	Ser	Val	Thr	Trp	Ser	Glu	Ser	Gly	180	185	190
Gln	Asn	Val	Thr	Ala	Arg	Asn	Phe	Pro	Pro	Ser	Gln	Asp	Ala	Ser	Gly	195	200	205
Asp	Leu	Tyr	Thr	Thr	Ser	Ser	Gln	Leu	Thr	Leu	Pro	Ala	Thr	Gln	Cys	210	215	220
Pro	Asp	Gly	Lys	Ser	Val	Thr	Cys	His	Val	Lys	His	Tyr	Thr	Asn	Pro	225	230	235
Ser	Gln	Asp	Val	Thr	Val	Pro	Cys	Pro	Val	Pro	Pro	Pro	Pro	Pro	Cys	245	250	255
Cys	His	Pro	Arg	Leu	Ser	Leu	His	Arg	Pro	Ala	Leu	Glu	Asp	Leu	Leu	260	265	270
Leu	Gly	Ser	Glu	Ala	Asn	Leu	Thr	Cys	Thr	Leu	Thr	Gly	Leu	Arg	Asp	275	280	285
Ala	Ser	Gly	Ala	Thr	Phe	Thr	Trp	Thr	Pro	Ser	Ser	Gly	Lys	Ser	Ala	290	295	300
Val	Gln	Gly	Pro	Pro	Glu	Arg	Asp	Leu	Cys	Gly	Cys	Tyr	Ser	Val	Ser	305	310	315
Ser	Val	Leu	Pro	Gly	Cys	Ala	Gln	Pro	Trp	Asn	His	Gly	Glu	Thr	Phe	325	330	335
Thr	Cys	Thr	Ala	Ala	His	Pro	Glu	Leu	Lys	Thr	Pro	Leu	Thr	Ala	Asn	340	345	350
Ile	Thr	Lys	Ser	Gly	Asn	Thr	Phe	Arg	Pro	Glu	Val	His	Leu	Leu	Pro	355	360	365
Pro	Pro	Ser	Glu	Glu	Leu	Ala	Leu	Asn	Glu	Leu	Val	Thr	Leu	Thr	Cys	370	375	380
Leu	Ala	Arg	Gly	Phe	Ser	Pro	Lys	Asp	Val	Leu	Val	Arg	Trp	Leu	Gln	385	390	395
Gly	Ser	Gln	Glu	Leu	Pro	Arg	Glu	Lys	Tyr	Leu	Thr	Trp	Ala	Ser	Arg	405	410	415
Gln	Glu	Pro	Ser	Gln	Gly	Thr	Thr	Thr	Phe	Ala	Val	Thr	Ser	Ile	Leu	420	425	430

106

Arg Val Ala Ala Glu Asp Trp Lys Lys Gly Asp Thr Phe Ser Cys Met
 435 440 445

Val Gly His Glu Ala Leu Pro Leu Ala Phe Thr Gln Lys Thr Ile Asp
 450 455 460

Arg Leu Ala Gly Lys Pro Thr His Val Asn Val Ser Val Val Met Ala
 465 470 475 480

Glu Val Asp Gly Thr Cys Tyr
 485

<210> 146
 <211> 294
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (93)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (97)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 146
 Met Met Val Gln Met Ile Ser Asp Ala Asn Thr Ala Gly Asn Gly Phe
 1 5 10 15

Met Ala Met Phe Ser Ala Ala Glu Pro Asn Glu Arg Gly Asp Gln Tyr
 20 25 30

Cys Gly Gly Leu Leu Asp Arg Pro Ser Gly Ser Phe Lys Thr Pro Asn
 35 40 45

Trp Pro Asp Arg Asp Tyr Pro Ala Gly Val Thr Cys Val Trp His Ile
 50 55 60

Val Ala Pro Lys Asn Gln Leu Ile Glu Leu Lys Phe Glu Lys Phe Asp
 65 70 75 80

Val Glu Arg Asp Asn Tyr Cys Arg Tyr Asp Tyr Val Xaa Val Phe Asn
 85 90 95

Xaa Gly Glu Val Asn Asp Ala Arg Arg Ile Gly Lys Tyr Cys Gly Asp
 100 105 110

Ser Pro Pro Ala Pro Ile Val Ser Glu Arg Asn Glu Leu Leu Ile Gln
 115 120 125

Phe Leu Ser Asp Leu Ser Leu Thr Ala Asp Gly Phe Ile Gly His Tyr
 130 135 140

Ile Phe Arg Pro Lys Lys Leu Pro Thr Thr Thr Glu Gln Pro Val Thr
 145 150 155 160

Thr Thr Phe Pro Val Thr Thr Gly Leu Lys Pro Thr Val Ala Leu Cys
 165 170 175

Gln Gln Lys Cys Arg Arg Thr Gly Thr Leu Glu Gly Asn Tyr Cys Ser
 180 185 190

Ser Asp Phe Val Leu Ala Gly Thr Val Ile Thr Thr Ile Thr Arg Asp

195 200 205
 Gly Ser Leu His Ala Thr Val Ser Ile Ile Asn Ile Tyr Lys Glu Gly
 210 215 220
 Asn Leu Ala Ile Gln Gln Ala Gly Lys Asn Met Ser Ala Arg Leu Thr
 225 230 235 240
 Val Val Cys Lys Gln Cys Pro Leu Leu Arg Arg Gly Leu Asn Tyr Ile
 245 250 255
 Ile Met Gly Gln Val Gly Glu Asp Gly Arg Gly Lys Ile Met Pro Asn
 260 265 270
 Ser Phe Ile Met Met Phe Lys Thr Lys Asn Gln Lys Leu Leu Asp Ala
 275 280 285
 Leu Lys Asn Lys Gln Cys
 290

<210> 147
 <211> 99
 <212> PRT
 <213> Homo sapiens

<400> 147
 Met Ala Val Trp Gly Asp Thr Glu Leu Ala Ala Gly Val Phe Cys Phe
 1 5 10 15
 Phe Leu Phe Phe Cys Phe Leu Tyr Leu Ser Gly Thr Trp Asn Ala Ser
 20 25 30
 Lys Thr Glu Leu Phe Thr Pro Leu Glu Arg Glu Leu Lys Pro Gly His
 35 40 45
 Pro Ser Gly Met Leu Ser Gly Ser His Pro His Gly Ala Gln Gln Ala
 50 55 60
 Lys Ser Thr Gly Leu Lys Leu Ser Leu Pro Ala Gln Gln Ser Glu Val
 65 70 75 80
 Asp Leu Gly Cys Ser Ser Leu Val Trp Gly Gly Ala Ser Ala Ile Thr
 85 90 95
 Glu Ala Leu

<210> 148
 <211> 265
 <212> PRT
 <213> Homo sapiens

<400> 148
 Met Gly Gly Gln Val Ala Gly Val Tyr Ala Ala Tyr Tyr Pro Ser Asp
 1 5 10 15
 Val Ser Ser Leu Cys Leu Val Cys Pro Ala Gly Leu Gln Tyr Ser Thr
 20 25 30
 Asp Asn Gln Phe Val Gln Arg Leu Lys Glu Leu Gln Gly Ser Ala Ala
 35 40 45
 Val Glu Lys Ile Pro Leu Ile Pro Ser Thr Pro Glu Glu Met Ser Glu
 50 55 60

Met Leu Gln Leu Cys Ser Tyr Val Arg Phe Lys Val Pro Gln Gln Ile
 65 70 75 80
 Leu Gln Gly Leu Val Asp Val Arg Ile Pro His Asn Asn Phe Tyr Arg
 85 90 95
 Lys Leu Phe Leu Glu Ile Val Ser Glu Lys Ser Arg Tyr Ser Leu His
 100 105 110
 Gln Asn Met Asp Lys Ile Lys Val Pro Thr Gln Ile Ile Trp Gly Lys
 115 120 125
 Gln Asp Ala Gly Ala Gly Cys Val Trp Gly Arg His Val Gly Gln Val
 130 135 140
 Asn Cys Gln Leu Pro Gly Gly Ala Ser Gly Lys Leu Trp Ala Leu Ser
 145 150 155 160
 Ser Asp Gly Lys Thr Gln Glu Asp Ser Gln Ala His Asn Arg Leu Phe
 165 170 175
 Ser Phe Cys Ala Gln His Arg Gln Gln Glu Ala Gly Leu Arg Pro
 180 185 190
 Arg Leu Gln Pro Ala Phe Cys Thr Gln His Leu Leu Pro Ser Pro Lys
 195 200 205
 Ser Asp Ala Ala Thr Thr Leu Arg Asp Pro Ala Pro Asn Ala Val Gly
 210 215 220
 Ala Pro Val Thr Leu Arg Lys Pro Val Pro Tyr Pro Trp Tyr Pro Arg
 225 230 235 240
 Phe Pro Arg Ala Leu Gly Thr Thr Arg Lys Pro Pro Arg Tyr Phe Ser
 245 250 255
 Gln Asn Arg Asn Ser Tyr Gly Thr Lys
 260 265

<210> 149
 <211> 206
 <212> PRT
 <213> Homo sapiens

<400> 149
 Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu
 1 5 10 15
 Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys
 20 25 30
 Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp
 35 40 45
 Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Pro Ala
 50 55 60
 Ile Pro Gly Ile Arg Gly Pro Lys Gly Arg Tyr Lys Gln Lys Phe Gln
 65 70 75 80
 Ser Val Phe Thr Val Thr Arg Gln Thr His Gln Pro Pro Ala Pro Asn
 85 90 95
 Ser Leu Ile Arg Phe Asn Ala Val Leu Thr Asn Pro Gln Gly Asp Tyr

109

100	105	110
Asp Thr Ser Thr Gly Lys Phe Thr Cys Lys Val Pro Gly Leu Tyr Tyr		
115	120	125
Phe Val Tyr His Ala Ser His Thr Ala Asn Leu Cys Val Leu Leu Tyr		
130	135	140
Arg Ser Gly Val Lys Val Val Thr Phe Cys Gly His Thr Ser Lys Thr		
145	150	155
Asn Gln Val Asn Ser Gly Gly Val Leu Leu Arg Leu Gln Val Gly Glu		
165	170	175
Glu Val Trp Leu Ala Val Asn Asp Tyr Tyr Asp Met Val Gly Ile Gln		
180	185	190
Gly Ser Asp Ser Val Phe Ser Gly Phe Leu Leu Phe Pro Asp		
195	200	205

<210> 150

<211> 234

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (120)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 150

Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp Leu Ser		
1	5	10
Gly Ala Arg Cys Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser		
20	25	30
Ala Ser Leu Gly Asp Ser Val Thr Ile Thr Cys Gln Ala Ser Gln Asp		
35	40	45
Ile Ala Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Pro Pro		
50	55	60
Lys Leu Val Ile Phe Asp Gly Ser Ile Leu His Thr Gly Val Pro Ser		
65	70	75
Arg Phe Ser Gly Gly Gly Ser Gly Thr His Phe Thr Phe Thr Ile Asn		
85	90	95
Asn Leu Gln Pro Asp Asp Val Ala Thr Tyr Ser Cys Gln Gln Tyr Asn		
100	105	110
Thr Phe Pro Leu Thr Phe Gly Xaa Gly Thr Lys Val Glu Ile Lys Arg		
115	120	125
Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln		
130	135	140
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr		
145	150	155
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser		
165	170	175
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr		

110

180 185 190
 Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
 195 200 205
 His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
 210 215 220
 Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 225 230

 <210> 151
 <211> 208
 <212> PRT
 <213> Homo sapiens

 <400> 151
 Met Asp Val Gly Pro Ser Ser Leu Pro His Leu Gly Leu Lys Leu Leu
 1 5 10 15
 Leu Leu Leu Leu Leu Leu Pro Leu Arg Gly Gln Ala Asn Thr Gly Cys
 20 25 30
 Tyr Gly Ile Pro Gly Met Pro Gly Leu Pro Gly Ala Pro Gly Lys Asp
 35 40 45
 Gly Tyr Asp Gly Leu Pro Gly Pro Lys Gly Glu Pro Gly Ile Pro Ala
 50 55 60
 Ile Pro Gly Ile Arg Gly Pro Lys Gly Gln Lys Gly Glu Pro Gly Leu
 65 70 75 80
 Pro Gly His Pro Gly Lys Asn Gly Pro Met Gly Pro Pro Gly Met Pro
 85 90 95
 Gly Val Pro Gly Pro Met Gly Ile Pro Gly Glu Pro Gly Glu Glu Gly
 100 105 110
 Arg Tyr Lys Gln Lys Phe Gln Ser Val Phe Thr Val Thr Arg Gln Thr
 115 120 125
 His Gln Pro Pro Ala Pro Asn Ser Leu Ile Arg Phe Asn Ala Val Leu
 130 135 140
 Thr Asn Pro Gln Glu Ile Met Thr Arg Ala Leu Ala Ser Ser Pro Ala
 145 150 155 160
 Lys Ser Pro Ala Ser Thr Thr Leu Ser Thr Thr Arg Arg Ile Gln Pro
 165 170 175
 Thr Cys Ala Cys Cys Cys Thr Ala Ala Ala Ser Lys Trp Ser Pro Ser
 180 185 190
 Val Ala Thr Arg Pro Lys Pro Ile Arg Ser Thr Arg Ala Val Cys Cys
 195 200 205

<210> 152
 <211> 235
 <212> PRT
 <213> Homo sapiens

111

<400> 152

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
 1 5 10 15
 Leu Arg Gly Ala Arg Cys Asp Met Gln Met Thr Gln Ser Pro Ser Ser
 20 25 30
 Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Thr Ser
 35 40 45
 Gln Ser Ile Gly Lys Phe Leu Asn Trp Tyr Gln Gln Lys Pro Gly Gln
 50 55 60
 Ala Pro Lys Leu Leu Ile Ser Gly Ala Ser Ile Leu Gln Thr Gly Val
 65 70 75 80
 Pro Ser Arg Phe Ser Gly Ser Gly Ser Ala Thr Tyr Phe Thr Leu Thr
 85 90 95
 Ile Asn Asp Leu His Pro Glu Asp Ser Ala Thr Tyr Tyr Cys Gln Gln
 100 105 110
 Asp Tyr Thr Thr Pro Leu Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
 115 120 125
 Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
 130 135 140
 Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
 145 150 155 160
 Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
 165 170 175
 Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
 180 185 190
 Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
 195 200 205
 Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
 210 215 220
 Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
 225 230 235

<210> 153

<211> 287

<212> PRT

<213> Homo sapiens

<400> 153

Met Gly Ala Leu Arg Pro Thr Leu Leu Pro Pro Ser Leu Pro Leu Leu
 1 5 10 15
 Leu Leu Leu Met Leu Gly Met Gly Cys Trp Ala Arg Glu Val Leu Val
 20 25 30
 Pro Glu Gly Pro Leu Tyr Arg Val Ala Gly Thr Ala Val Ser Ile Ser
 35 40 45
 Cys Asn Val Thr Gly Tyr Glu Gly Pro Ala Gln Gln Asn Phe Glu Trp
 50 55 60
 Phe Leu Tyr Arg Pro Glu Ala Pro Asp Thr Ala Leu Gly Ile Val Ser

112

65					70					75					80
Thr	Lys	Asp	Thr	Gln	Phe	Ser	Tyr	Ala	Val	Phe	Lys	Ser	Arg	Val	Val
				85					90					95	
Ala	Gly	Glu	Val	Gln	Val	Gln	Arg	Leu	Gln	Gly	Asp	Ala	Val	Val	Leu
			100					105					110		
Lys	Ile	Ala	Arg	Leu	Gln	Ala	Gln	Asp	Ala	Gly	Ile	Tyr	Glu	Cys	His
		115					120					125			
Thr	Pro	Ser	Thr	Asp	Thr	Arg	Tyr	Leu	Gly	Ser	Tyr	Ser	Gly	Lys	Val
	130					135					140				
Glu	Leu	Arg	Val	Leu	Pro	Asp	Val	Leu	Gln	Val	Ser	Ala	Ala	Pro	Pro
145					150					155					160
Gly	Pro	Arg	Gly	Arg	Gln	Ala	Pro	Thr	Ser	Pro	Pro	Arg	Met	Thr	Val
				165					170					175	
His	Glu	Gly	Gln	Glu	Leu	Ala	Leu	Gly	Cys	Leu	Ala	Arg	Thr	Ser	Thr
			180					185					190		
Gln	Lys	His	Thr	His	Leu	Ala	Val	Ser	Phe	Gly	Arg	Ser	Val	Pro	Glu
		195					200					205			
Ala	Pro	Val	Gly	Arg	Ser	Thr	Leu	Gln	Glu	Val	Val	Gly	Ile	Arg	Ser
	210					215					220				
Asp	Leu	Ala	Val	Glu	Ala	Gly	Ala	Pro	Tyr	Ala	Glu	Arg	Leu	Ala	Ala
225					230					235					240
Gly	Glu	Leu	Arg	Leu	Gly	Lys	Glu	Gly	Thr	Asp	Arg	Tyr	Arg	Met	Val
				245					250					255	
Val	Gly	Gly	Ala	Gln	Ala	Gly	Asp	Ala	Gly	Thr	Tyr	His	Cys	Thr	Ala
			260					265					270		
Ala	Glu	Trp	Ile	Gln	Asp	Pro	Asp	Gly	Ser	Trp	Ala	Gln	Ile	Ala	
	275						280					285			

<210> 154

<211> 203

<212> PRT

<213> Homo sapiens

<400> 154

Met	Gly	Leu	Ile	Leu	Thr	Val	Val	Gly	Val	His	Asn	Asp	Thr	Val	Asp
1				5					10					15	
Arg	Val	Val	Pro	Gln	Phe	Gln	His	Leu	Ile	Tyr	Gly	Cys	Val	Ala	Gln
			20				25						30		
Glu	His	Ile	His	Thr	Leu	Val	Leu	Pro	Glu	Arg	Asn	Thr	Val	Leu	Gly
		35					40					45			
Val	Asp	Gly	Val	Gly	Ser	Ser	Glu	Asp	Pro	Ser	Val	Pro	Gln	Gln	Gly
	50					55					60				
Pro	Ala	Pro	Thr	Ala	Val	Asp	Thr	Gly	Glu	Gly	Leu	Pro	Gly	Glu	Val
65					70					75					80
Ala	Gln	Leu	Gly	Ser	Gly	Arg	Thr	Glu	Gly	Arg	Leu	Ile	Leu	Gly	Asn
				85					90					95	

113

Gly Gly Asp Trp Pro Ser Ala Asp Arg His Thr Leu Lys Asn Leu Leu
 100 105 110
 Pro Ile Leu Ser Val Phe Pro Gly Pro Trp Gly Cys Thr Gly Glu Cys
 115 120 125
 Pro Cys Cys Arg Gly Leu Ile Ile Gly Leu Leu Ala Val Val Leu Asp
 130 135 140
 Leu Gly Arg Val Val Ser Arg Cys Val Asp Gly Leu Arg Ala Pro Ala
 145 150 155 160
 Gly Leu Ala Asp Gly Leu Thr Ile Val His Ser His Gly Leu Val Glu
 165 170 175
 Gly Gln Glu Ala Leu Val Glu Val Gly Ser Leu Val Leu Arg Gly Arg
 180 185 190
 Leu Cys Ala Glu Gly Gln Pro Gln Thr Pro Pro
 195 200

<210> 155
 <211> 2165
 <212> PRT
 <213> Homo sapiens

<400> 155
 Met Arg Ser Ile Gly Gly Ser Phe His Leu Leu Gln Pro Val Val Ala
 1 5 10 15
 Ala Leu Ile Leu Leu Val Val Cys Leu Val Tyr Ala Leu Gln Ser Gly
 20 25 30
 Ser Gly Thr Ile Ser Glu Phe Ser Ser Asp Val Leu Phe Ser Arg Ala
 35 40 45
 Lys Tyr Ser Gly Val Pro Val His His Ser Arg Trp Arg Gln Asp Ala
 50 55 60
 Gly Ile His Val Ile Asp Ser His His Ile Val Arg Arg Asp Ser Tyr
 65 70 75 80
 Gly Arg Arg Gly Lys Arg Asp Val Thr Ser Thr Asp Arg Arg Arg Arg
 85 90 95
 Leu Gln Gly Val Ala Arg Asp Cys Gly His Ala Cys His Leu Arg Leu
 100 105 110
 Arg Ser Asp Asp Ala Val Tyr Ile Val His Leu His Arg Trp Asn Gln
 115 120 125
 Ile Pro Asp Ser His Asn Lys Ser Val Pro His Phe Ser Asn Ser Asn
 130 135 140
 Phe Ala Pro Met Val Leu Tyr Leu Asp Ser Glu Glu Glu Val Arg Gly
 145 150 155 160
 Gly Met Ser Arg Thr Asp Pro Asp Cys Ile Tyr Arg Ala His Val Lys
 165 170 175
 Gly Val His Gln His Ser Ile Val Asn Leu Cys Asp Ser Glu Asp Gly
 180 185 190
 Leu Tyr Gly Met Leu Ala Leu Pro Ser Gly Ile His Thr Val Glu Pro
 195 200 205

Ile Ile Ser Gly Asn Gly Thr Glu His Asp Gly Ala Ser Arg His Arg
 210 215 220
 Gln His Leu Val Arg Lys Phe Asp Pro Met His Phe Lys Ser Phe Asp
 225 230 235 240
 His Leu Asn Ser Thr Ser Val Asn Glu Thr Glu Thr Thr Val Ala Thr
 245 250 255
 Trp Gln Asp Gln Trp Glu Asp Val Ile Glu Arg Lys Ala Arg Ser Arg
 260 265 270
 Arg Ala Ala Asn Ser Trp Asp His Tyr Val Glu Val Leu Val Val Ala
 275 280 285
 Asp Thr Lys Met Tyr Glu Tyr His Gly Arg Ser Leu Glu Asp Tyr Val
 290 295 300
 Leu Thr Leu Phe Ser Thr Val Ala Ser Ile Tyr Arg His Gln Ser Leu
 305 310 315 320
 Arg Ala Ser Ile Asn Val Val Val Val Lys Leu Ile Val Leu Lys Thr
 325 330 335
 Glu Asn Ala Gly Pro Arg Ile Thr Gln Asn Ala Gln Gln Thr Leu Gln
 340 345 350
 Asp Phe Cys Arg Trp Gln Gln Tyr Tyr Asn Asp Pro Asp Asp Ser Ser
 355 360 365
 Val Gln His His Asp Val Ala Ile Leu Leu Thr Arg Lys Asp Ile Cys
 370 375 380
 Arg Ser Gln Gly Lys Cys Asp Thr Leu Gly Leu Ala Glu Leu Gly Thr
 385 390 395 400
 Met Cys Asp Met Gln Lys Ser Cys Ala Ile Ile Glu Asp Asn Gly Leu
 405 410 415
 Ser Ala Ala Phe Thr Ile Ala His Glu Leu Gly His Val Phe Ser Ile
 420 425 430
 Pro His Asp Asp Glu Arg Lys Cys Ser Thr Tyr Met Pro Val Asn Lys
 435 440 445
 Val Cys Lys Phe Gln Ser Thr Lys Phe Asp Lys Thr Gln Phe Gln Asn
 450 455 460
 Asn Phe His Ile Met Ala Pro Thr Leu Glu Tyr Asn Thr His Pro Trp
 465 470 475 480
 Ser Trp Ser Pro Cys Ser Ala Gly Met Leu Glu Arg Phe Leu Glu Asn
 485 490 495
 Asn Arg Gly Gln Thr Gln Cys Leu Phe Asp Gln Pro Val Glu Arg Arg
 500 505 510
 Tyr Tyr Glu Asp Val Phe Val Arg Asp Glu Pro Gly Lys Lys Tyr Asp
 515 520 525
 Ala His Gln Gln Cys Lys Phe Val Phe Gly Pro Ala Ser Glu Leu Cys
 530 535 540
 Pro Tyr Met Pro Thr Cys Arg Arg Leu Trp Cys Ala Thr Phe Tyr Gly
 545 550 555 560

Ser Gln Met Gly Cys Arg Thr Gln His Met Pro Trp Ala Asp Gly Thr
 565 570 575
 Pro Cys Asp Glu Ser Arg Ser Met Phe Cys His His Gly Ala Cys Val
 580 585 590
 Arg Leu Ala Pro Glu Ser Leu Thr Lys Ile Asp Gly Gln Trp Gly Asp
 595 600 605
 Trp Arg Ser Trp Gly Glu Cys Ser Arg Thr Cys Gly Gly Gly Val Gln
 610 615 620
 Lys Gly Leu Arg Asp Cys Asp Ser Pro Lys Pro Arg Asn Gly Gly Lys
 625 630 635 640
 Tyr Cys Val Gly Gln Arg Glu Arg Tyr Arg Ser Cys Asn Thr Gln Glu
 645 650 655
 Cys Pro Trp Asp Thr Gln Pro Tyr Arg Glu Val Gln Cys Ser Glu Phe
 660 665 670
 Asn Asn Lys Asp Ile Gly Ile Gln Gly Val Ala Ser Thr Asn Thr His
 675 680 685
 Trp Val Pro Lys Tyr Ala Asn Val Ala Pro Asn Glu Arg Cys Lys Leu
 690 695 700
 Tyr Cys Arg Leu Ser Gly Ser Ala Ala Phe Tyr Leu Leu Arg Asp Lys
 705 710 715 720
 Val Val Asp Gly Thr Pro Cys Asp Arg Asn Gly Asp Asp Ile Cys Val
 725 730 735
 Ala Gly Ala Cys Met Pro Ala Gly Cys Asp His Gln Leu His Ser Thr
 740 745 750
 Leu Arg Arg Asp Lys Cys Gly Val Cys Gly Gly Asp Asp Ser Ser Cys
 755 760 765
 Lys Val Val Lys Gly Thr Phe Asn Glu Gln Gly Thr Phe Gly Tyr Asn
 770 775 780
 Glu Val Met Lys Ile Pro Ala Gly Ser Ala Asn Ile Asp Ile Arg Gln
 785 790 795 800
 Lys Gly Tyr Asn Asn Met Lys Glu Asp Asp Asn Tyr Leu Ser Leu Arg
 805 810 815
 Ala Ala Asn Gly Glu Phe Leu Leu Asn Gly His Phe Gln Val Ser Leu
 820 825 830
 Ala Arg Gln Gln Ile Ala Phe Gln Asp Thr Val Leu Glu Tyr Ser Gly
 835 840 845
 Ser Asp Ala Ile Ile Glu Arg Ile Asn Gly Thr Gly Pro Ile Arg Ser
 850 855 860
 Asp Ile Tyr Val His Val Leu Ser Val Gly Ser His Pro Pro Asp Ile
 865 870 875 880
 Ser Tyr Glu Tyr Met Thr Ala Ala Val Pro Asn Ala Val Ile Arg Pro
 885 890 895
 Ile Ser Ser Ala Leu Tyr Leu Trp Arg Val Thr Asp Thr Trp Thr Glu
 900 905 910

Cys Asp Arg Ala Cys Arg Gly Gln Gln Ser Gln Lys Leu Met Cys Leu
 915 920 925
 Asp Met Ser Thr His Arg Gln Ser His Asp Arg Asn Cys Gln Asn Val
 930 935 940
 Leu Lys Pro Lys Gln Ala Thr Arg Met Cys Asn Ile Asp Cys Ser Thr
 945 950 955 960
 Arg Trp Ile Thr Glu Asp Val Ser Ser Cys Ser Ala Lys Cys Gly Ser
 965 970 975
 Gly Gln Lys Arg Gln Arg Val Ser Cys Val Lys Met Glu Gly Asp Arg
 980 985 990
 Gln Thr Pro Ala Ser Glu His Leu Cys Asp Arg Asn Ser Lys Pro Ser
 995 1000 1005
 Asp Ile Ala Ser Cys Tyr Ile Asp Cys Ser Gly Arg Lys Trp Asn Tyr
 1010 1015 1020
 Gly Glu Trp Thr Ser Cys Ser Glu Thr Cys Gly Ser Asn Gly Lys Met
 1030 1035 1040
 His Arg Lys Ser Tyr Cys Val Asp Asp Ser Asn Arg Arg Val Asp Glu
 1045 1050 1055
 Ser Leu Cys Gly Arg Glu Gln Lys Glu Ala Thr Glu Arg Glu Cys Asn
 1060 1065 1070
 Arg Ile Pro Cys Pro Arg Trp Val Tyr Gly His Trp Ser Glu Cys Ser
 1075 1080 1085
 Arg Ser Cys Asp Gly Gly Val Lys Met Arg His Ala Gln Cys Leu Asp
 1090 1095 1100
 Ala Ala Asp Arg Glu Thr His Thr Ser Arg Cys Gly Pro Ala Gln Thr
 1110 1115 1120
 Gln Glu His Cys Asn Glu His Ala Cys Thr Trp Trp Gln Phe Gly Val
 1125 1130 1135
 Trp Ser Asp Cys Ser Ala Lys Cys Gly Asp Gly Val Gln Tyr Arg Asp
 1140 1145 1150
 Ala Asn Cys Thr Asp Arg His Arg Ser Val Leu Pro Glu His Arg Cys
 1155 1160 1165
 Leu Lys Met Glu Lys Ile Ile Thr Lys Pro Cys His Arg Glu Ser Cys
 1170 1175 1180
 Pro Lys Tyr Lys Leu Gly Glu Trp Ser Gln Cys Ser Val Ser Cys Glu
 1190 1195 1200
 Asp Gly Trp Ser Ser Arg Arg Val Ser Cys Val Ser Gly Asn Gly Thr
 1205 1210 1215
 Glu Val Asp Met Ser Leu Cys Gly Thr Ala Ser Asp Arg Pro Ala Ser
 1220 1225 1230
 His Gln Thr Cys Asn Leu Gly Thr Cys Pro Phe Trp Arg Asn Thr Asp
 1235 1240 1245
 Trp Ser Ala Cys Ser Val Ser Cys Gly Ile Gly His Arg Glu Arg Thr
 1250 1255 1260

Thr Glu Cys Ile Tyr Arg Glu Gln Ser Val Asp Ala Ser Phe Cys Gly
 1270 1275 1280
 Asp Thr Lys Met Pro Glu Thr Ser Gln Thr Cys His Leu Leu Pro Cys
 1285 1290 1295
 Thr Ser Trp Lys Pro Ser His Trp Ser Pro Cys Ser Val Thr Cys Gly
 1300 1305 1310
 Ser Gly Ile Gln Thr Arg Ser Val Ser Cys Thr Arg Gly Ser Glu Gly
 1315 1320 1325
 Thr Ile Val Asp Glu Tyr Phe Cys Asp Arg Asn Thr Arg Pro Arg Leu
 1330 1335 1340
 Lys Lys Thr Cys Glu Lys Asp Thr Cys Asp Gly Pro Arg Val Leu Gln
 1350 1355 1360
 Lys Leu Gln Ala Asp Val Pro Pro Ile Arg Trp Ala Thr Gly Pro Trp
 1365 1370 1375
 Thr Ala Cys Ser Ala Thr Cys Gly Asn Gly Thr Gln Arg Arg Leu Leu
 1380 1385 1390
 Lys Cys Arg Asp His Val Arg Asp Leu Pro Asp Glu Tyr Cys Asn His
 1395 1400 1405
 Leu Asp Lys Glu Val Ser Thr Arg Asn Cys Arg Leu Arg Asp Cys Ser
 1410 1415 1420
 Tyr Trp Lys Met Ala Glu Trp Glu Glu Cys Pro Ala Thr Cys Gly Thr
 1430 1435 1440
 His Val Gln Gln Ser Arg Asn Val Thr Cys Val Ser Ala Glu Asp Gly
 1445 1450 1455
 Gly Arg Thr Ile Leu Lys Asp Val Asp Cys Asp Val Gln Lys Arg Pro
 1460 1465 1470
 Thr Ser Ala Arg Asn Cys Arg Leu Glu Pro Cys Pro Lys Gly Glu Glu
 1475 1480 1485
 His Ile Gly Ser Trp Ile Ile Gly Asp Trp Ser Lys Cys Ser Ala Ser
 1490 1495 1500
 Cys Gly Gly Gly Trp Arg Arg Arg Ser Val Ser Cys Thr Ser Ser Ser
 1510 1515 1520
 Cys Asp Glu Thr Arg Lys Pro Lys Met Phe Asp Lys Cys Asn Glu Glu
 1525 1530 1535
 Leu Cys Pro Pro Leu Thr Asn Asn Ser Trp Gln Ile Ser Pro Trp Thr
 1540 1545 1550
 His Cys Ser Val Ser Cys Gly Gly Gly Val Gln Arg Arg Lys Ile Trp
 1555 1560 1565
 Cys Glu Asp Val Leu Ser Gly Arg Lys Gln Asp Asp Ile Glu Cys Ser
 1570 1575 1580
 Glu Ile Lys Pro Arg Glu Gln Arg Asp Cys Glu Met Pro Pro Cys Arg
 1590 1595 1600
 Ser His Tyr His Asn Lys Thr Ser Ser Ala Ser Met Thr Ser Leu Ser
 1605 1610 1615

Ser Ser Asn Ser Asn Thr Thr Ser Ser Ala Ser Ala Ser Ser Leu Pro
 1620 1625 1630
 Ile Leu Pro Pro Val Val Ser Trp Gln Thr Ser Ala Trp Ser Ala Cys
 1635 1640 1645
 Ser Ala Lys Cys Gly Arg Gly Thr Lys Arg Arg Val Val Glu Cys Val
 1650 1655 1660
 Asn Pro Ser Leu Asn Val Thr Val Ala Ser Thr Glu Cys Asp Gln Thr
 1670 1675 1680
 Lys Lys Pro Val Glu Glu Val Arg Cys Arg Thr Lys His Cys Pro Arg
 1685 1690 1695
 Trp Lys Thr Thr Thr Trp Ser Ser Cys Ser Val Thr Cys Gly Arg Gly
 1700 1705 1710
 Ile Arg Arg Arg Glu Val Gln Cys Tyr Arg Gly Arg Lys Asn Leu Val
 1715 1720 1725
 Ser Asp Ser Glu Cys Asn Pro Lys Thr Lys Leu Asn Ser Val Ala Asn
 1730 1735 1740
 Cys Phe Pro Val Ala Cys Pro Ala Tyr Arg Trp Asn Val Thr Pro Trp
 1750 1755 1760
 Ser Lys Cys Lys Asp Glu Cys Ala Arg Gly Gln Lys Gln Thr Arg Arg
 1765 1770 1775
 Val His Cys Ile Ser Thr Ser Gly Lys Arg Ala Ala Pro Arg Met Cys
 1780 1785 1790
 Glu Leu Ala Arg Ala Pro Thr Ser Ile Arg Glu Cys Asp Thr Ser Asn
 1795 1800 1805
 Cys Pro Tyr Glu Trp Val Pro Gly Asp Trp Gln Thr Cys Ser Lys Ser
 1810 1815 1820
 Cys Gly Glu Gly Val Gln Thr Arg Glu Val Arg Cys Arg Arg Lys Ile
 1830 1835 1840
 Asn Phe Asn Ser Thr Ile Pro Ile Ile Phe Met Leu Glu Asp Glu Pro
 1845 1850 1855
 Ala Val Pro Lys Glu Lys Cys Glu Leu Phe Pro Lys Pro Asn Glu Ser
 1860 1865 1870
 Gln Thr Cys Glu Leu Asn Pro Cys Asp Ser Glu Phe Lys Trp Ser Phe
 1875 1880 1885
 Gly Pro Trp Gly Glu Cys Ser Lys Asn Cys Gly Gln Gly Ile Arg Arg
 1890 1895 1900
 Arg Arg Val Lys Cys Val Ala Asn Asp Gly Arg Arg Val Glu Arg Val
 1910 1915 1920
 Lys Cys Thr Thr Lys Lys Pro Arg Arg Thr Gln Tyr Cys Phe Glu Arg
 1925 1930 1935
 Asn Cys Leu Pro Ser Thr Cys Gln Glu Leu Lys Ser Gln Asn Val Lys
 1940 1945 1950
 Ala Lys Asp Gly Asn Tyr Thr Ile Leu Leu Asp Gly Phe Thr Ile Glu
 1955 1960 1965

Ile Tyr Cys His Arg Met Asn Ser Thr Ile Pro Lys Ala Tyr Leu Asn
 1970 1975 1980
 Val Asn Pro Arg Thr Asn Phe Ala Glu Val Tyr Gly Lys Lys Leu Ile
 1990 1995 2000
 Tyr Pro His Thr Cys Pro Phe Asn Gly Asp Arg Asn Asp Ser Cys His
 2005 2010 2015
 Cys Ser Glu Asp Gly Asp Ala Ser Ala Gly Leu Thr Arg Phe Asn Lys
 2020 2025 2030
 Val Arg Ile Asp Leu Leu Asn Arg Lys Phe His Leu Ala Asp Tyr Thr
 2035 2040 2045
 Phe Ala Lys Arg Glu Tyr Gly Val His Val Pro Tyr Gly Thr Ala Gly
 2050 2055 2060
 Asp Cys Tyr Ser Met Lys Asp Cys Pro Gln Gly Ile Phe Ser Ile Asp
 2070 2075 2080
 Leu Lys Ser Ala Gly Leu Lys Leu Val Asp Asp Leu Asn Trp Glu Asp
 2085 2090 2095
 Gln Gly His Arg Thr Ser Ser Arg Ile Asp Arg Phe Tyr Asn Asn Ala
 2100 2105 2110
 Lys Val Ile Gly His Cys Gly Gly Phe Cys Gly Lys Cys Ser Pro Glu
 2115 2120 2125
 Arg Tyr Lys Gly Leu Ile Phe Glu Val Asn Thr Lys Leu Leu Asn His
 2130 2135 2140
 Val Lys Asn Gly Gly His Ile Asp Asp Glu Leu Asp Asp Asp Gly Phe
 2150 2155 2160
 Ser Gly Asp Met Asp
 2165

<210> 156
 <211> 446
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 <213> Homo sapiens

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<400> 156
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AGTTGCAAAC CTTAGCGGTG GGTCTCAAGG GGAATTCAGC TGCCTTGCTC AGAATGAGGC 120
AGGGGTGCTC ATGCAGAAGG CATCTTTAGT GATCCAAGAT TACTGGTGGT CTGTGGACAG 180
ACTGGCAACC TGCTCAGCCT CCTGTGGTAA CCGGGGGGTT CAGCAGCCCC GCTTGAGGTG 240
CCTGCTGAAC AGCACGGAGG TCAACCTGCG CCACTGCGCA GGAAGGTTT GCCCTGCGGT 300
GCAGCCCATC GTGTGCAACC GGAGAGACTG CCCTTCTCGG TGGATGGTGA CCTCCTGGTC 360
TGCCTGTACC CGGAGCTGTN GGGGAGGTGT NCANACCCCA NGGTGACCTG TCAAAAGCTG 420
AAAAGCCTNT GGGATCTCCA CCCCTG 446

<210> 157
<211> 354
<212> DNA
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<220>
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AGCAGCAGTG TGTGGAGTGG GCCTTCTCCA GCTGGGGNCA GTGCAATGGG CCTTG CATCG 60
GGNCTCACCT AGCTGTGCAA CACAGACAAG TCTTCTGNCA GACACGGGAT GGCATCACCT 120
TACCATCAGA GCAGTGCAGT GCTCTTCCGA GGCTGTGAG CACCCAGAAC TGCTGGTCAG 180
AGGCCTGCAG TGTACACTGG AGAGTCAGCC TGTGGACCCT GTGCACAGCT ACCTGTGGCA 240
ACTACGGCTT CCAGTCCCGG CGTGTGGAGT GTGTGCATGC NCGNACCAAC AAAGGCAGTG 300
NCTTGANCAC CTGTGCTACC TGGGGGACCC GGACTTGCCC AATTGGCAGC GCNG 354

<210> 158
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GGCAGAGGNG AAAA ACTCTA CCCTGGCCAC ACGAAGGACT CNCGCAACCN NCTCGGACAG 60

AACCTAAGCT TTCTTCATTN TATTTATTTA TTTCCCCCTC CCCACTCCAC ACACACCCTT 120

CCAACCTCCT CCANCTCCAC CTTCAAGCAT AAGGACGTCC GCNTGTTTTT TCTTTCAGTT 180

AGCTGGAGGA CAGGATGTTG GGAAAGGAAA GGACAGATGT CTAAAGGAGG TTGCAGAGCA 240

GGCCAGGCAG ACAGTGGGGG GGCTTCCTTN GANGGNGCTT TCCTCCCTCC CAAANCTGGG 300

GGTTTTTCAAA GACCTTNG 318

<210> 159

<211> 442

<212> DNA

<213> Homo sapiens

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<222> (98)

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GGCAGAGGNA CTTCCCCAGT GACTCTCTCG CCTCATAAAC ACGTGTCTGG CTTCAGCAGC	60
TCCCTGCGGA CCTCCTCCAC CGGGGACGCC GGGGGAGNCT CTCGAAGGCC ACACCGCAAG	120
CCCACCATCC TGCGGCAAGA TCTCAGCGGC CCAGCAGCTC TCAGCCTCGG AGGTGGTCAC	180
CCACCTGGGG NCAGACGGTG GCCCTGGCCA GCGGGACACT GAGTGTCTTT CTGCACTGTG	240
AGGCCATCGG CAACCCAAGG CCTTACCATC AGNTGGGCCA GGAATGGGAG AAGGAAGTTT	300
CANTTCAGTG GACAGGATTC TTNTTACAGC CAGATGATTN CTTTACAGAT TTTGGGCACC	360
ATGGGAAGCA GATGTGGGTT TTTTACAATT TGCAATGGCC ANCAATGNCT TGGGNTAANG	420
ATTTTGTTC CATTGGCCTT NA	442

<210> 160
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 <212> DNA
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 CTGTGTCTTT CCTAGAAGCG CACTATCACA AACACAGGAG TGTTTTGCTC CTTTGTCTCC 120
 TCTTCCCAT CTATGTCCCT TTAGTCACAG TTAGGACAAA TGGGGAGGGG ACACCATGCT 180
 GAGGCAGAAA CTAGCCCAGA ACTCACTCAG TTCTTCTAGT GGGTGAGTGC AGAGAGAGAA 240
 GAACTCAGAT CACCACTAGG GAGAGGTAAA AAAGCAAACA AAGCAGGCTC TAAGGCACAC 300
 AACATTGCCA GAAAATGAGG AANGGAGGGG GAGGGAAGGG ACAGAAGCCA AAAGGGACCT 360
 NTNGGTGTTT CCCATNGGGG CAGGTTNAAC AGGGGTTTCC AGGTGCATGN GGCTCTGGGA 420
 CCACTTTGA 429

<210> 161
 <211> 50
 <212> PRT
 <213> Homo sapiens

<400> 161
 Asp Gly Leu Trp Asp Ala Trp Gly Pro Trp Ser Glu Cys Ser Arg Thr
 1 5 10 15
 Cys Gly Gly Gly Ala Ser Tyr Ser Leu Arg Arg Cys Leu Ser Ser Lys
 20 25 30
 Ser Cys Glu Gly Arg Asn Ile Arg Tyr Arg Thr Cys Ser Asn Val Asp
 35 40 45
 Cys Pro
 50

125

<210> 162
 <211> 60
 <212> PRT
 <213> Homo sapiens

<400> 162
 Trp Arg Glu Thr Asp Phe Phe Pro Cys Ser Ala Thr Cys Gly Gly Gly
 1 5 10 15
 Tyr Gln Leu Thr Ser Ala Glu Cys Tyr Asp Leu Arg Ser Asn Arg Val
 20 25 30
 Val Ala Asp Gln Tyr Cys His Tyr Tyr Pro Glu Asn Ile Lys Pro Lys
 35 40 45
 Pro Lys Leu Gln Glu Cys Asn Leu Asp Pro Cys Pro
 50 55 60

<210> 163
 <211> 59
 <212> PRT
 <213> Homo sapiens

<400> 163
 Trp Glu Ala Thr Pro Trp Thr Ala Cys Ser Ser Ser Cys Gly Gly Gly
 1 5 10 15
 Ile Gln Ser Arg Ala Val Ser Cys Val Glu Glu Asp Ile Gln Gly His
 20 25 30
 Val Thr Ser Val Glu Glu Trp Lys Cys Met Tyr Thr Pro Lys Met Pro
 35 40 45
 Ile Ala Gln Pro Cys Asn Ile Phe Asp Cys Pro
 50 55

<210> 164
 <211> 53
 <212> PRT
 <213> Homo sapiens

<400> 164
 Trp Leu Ala Gln Glu Trp Ser Pro Cys Thr Val Thr Cys Gly Gln Gly
 1 5 10 15
 Leu Arg Tyr Arg Val Val Leu Cys Ile Asp His Arg Gly Met His Thr
 20 25 30
 Gly Gly Cys Ser Pro Lys Thr Lys Pro His Ile Lys Glu Glu Cys Ile
 35 40 45
 Val Pro Thr Pro Cys
 50

<210> 165
 <211> 53
 <212> PRT
 <213> Homo sapiens

<400> 165
 Trp Ser Ala Cys Thr Val Thr Cys Gly Val Gly Thr Gln Val Arg Ile
 1 5 10 15

126

Val Arg Cys Gln Val Leu Leu Ser Phe Ser Gln Ser Val Ala Asp Leu
 20 25 30
 Pro Ile Asp Glu Cys Glu Gly Pro Lys Pro Ala Ser Gln Arg Ala Cys
 35 40 45
 Tyr Ala Gly Pro Cys
 50

<210> 166
 <211> 61
 <212> PRT
 <213> Homo sapiens

<400> 166
 Glu Leu Tyr Asp Trp Glu Tyr Glu Gly Phe Thr Lys Cys Ser Glu Ser
 1 5 10 15
 Cys Gly Gly Gly Val Gln Glu Ala Val Val Ser Cys Leu Asn Lys Gln
 20 25 30
 Thr Arg Glu Pro Ala Glu Glu Asn Leu Cys Val Thr Ser Arg Arg Pro
 35 40 45
 Pro Gln Leu Leu Lys Ser Cys Asn Leu Asp Pro Cys Pro
 50 55 60

<210> 167
 <211> 60
 <212> PRT
 <213> Homo sapiens

<400> 167
 Trp Glu Ile Gly Lys Trp Ser Pro Cys Ser Leu Thr Cys Gly Val Gly
 1 5 10 15
 Leu Gln Thr Arg Asp Val Phe Cys Ser His Leu Leu Ser Arg Glu Met
 20 25 30
 Asn Glu Thr Val Ile Leu Ala Asp Glu Leu Cys Arg Gln Pro Lys Pro
 35 40 45
 Ser Thr Val Gln Ala Cys Asn Arg Phe Asn Cys Pro
 50 55 60

<210> 168
 <211> 58
 <212> PRT
 <213> Homo sapiens

<400> 168
 Trp Tyr Pro Ala Gln Trp Gln Pro Cys Ser Arg Thr Cys Gly Gly Gly
 1 5 10 15
 Val Gln Lys Arg Glu Val Leu Cys Lys Gln Arg Met Ala Asp Gly Ser
 20 25 30
 Phe Leu Glu Leu Pro Glu Thr Phe Cys Ser Ala Ser Lys Pro Ala Cys
 35 40 45
 Gln Gln Ala Cys Lys Lys Asp Asp Cys Pro
 50 55

127

<210> 169
 <211> 58
 <212> PRT
 <213> Homo sapiens

<400> 169
 Trp Leu Leu Ser Asp Trp Thr Glu Cys Ser Thr Ser Cys Gly Glu Gly
 1 5 10 15
 Thr Gln Thr Arg Ser Ala Ile Cys Arg Lys Met Leu Lys Thr Gly Leu
 20 25 30
 Ser Thr Val Val Asn Ser Thr Leu Cys Pro Pro Leu Pro Phe Ser Ser
 35 40 45
 Ser Ile Arg Pro Cys Met Leu Ala Thr Cys
 50 55

<210> 170
 <211> 57
 <212> PRT
 <213> Homo sapiens

<400> 170
 Trp Trp Ser Val Asp Arg Leu Ala Thr Cys Ser Ala Ser Cys Gly Asn
 1 5 10 15
 Arg Gly Val Gln Gln Pro Arg Leu Arg Cys Leu Leu Asn Ser Thr Glu
 20 25 30
 Val Asn Pro Ala His Cys Ala Gly Lys Val Arg Pro Ala Val Gln Pro
 35 40 45
 Ile Ala Cys Asn Arg Arg Asp Cys Pro
 50 55

<210> 171
 <211> 59
 <212> PRT
 <213> Homo sapiens

<400> 171
 Trp Met Val Thr Ser Trp Ser Ala Cys Thr Arg Ser Cys Gly Gly Gly
 1 5 10 15
 Val Gln Thr Arg Arg Val Thr Cys Gln Lys Leu Lys Ala Ser Gly Ile
 20 25 30
 Ser Thr Pro Val Ser Asn Asp Met Cys Thr Gln Val Ala Lys Arg Pro
 35 40 45
 Val Asp Thr Gln Ala Cys Asn Gln Gln Leu Cys
 50 55

<210> 172
 <211> 58
 <212> PRT
 <213> Homo sapiens

<400> 172
 Trp Ala Phe Ser Ser Trp Gly Gln Cys Asn Gly Pro Cys Ile Gly Pro

1					5					10					15				
His	Leu	Ala	Val	Gln	His	Arg	Gln	Val	Phe	Cys	Gln	Thr	Arg	Asp	Gly				
				20					25					30					
Ile	Thr	Leu	Pro	Ser	Glu	Gln	Cys	Ser	Ala	Leu	Pro	Arg	Pro	Val	Ser				
				35					40					45					
Thr	Gln	Asn	Cys	Trp	Ser	Glu	Ala	Cys	Ser										
				50					55										

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<210> 173
<211> 56
<212> PRT
<213> Homo sapiens
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<400> 173
Trp Arg Val Ser Leu Trp Thr Leu Cys Thr Ala Thr Cys Gly Asn Tyr
  1          5          10          15
Gly Phe Gln Ser Arg Arg Val Glu Cys Val His Ala Arg Thr Asn Lys
          20          25          30
Ala Val Pro Glu His Leu Cys Ser Trp Gly Pro Arg Pro Ala Asn Trp
          35          40          45
Gln Arg Cys Asn Ile Thr Pro Cys
  50          55

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<210> 174
<211> 138
<212> PRT
<213> Homo sapiens
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<400> 174															
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1				5					10					15	
Val	Lys	His	His	Gly	Gln	Phe	Tyr	Glu	Trp	Leu	Pro	Val	Ser	Asn	Asp
			20					25					30		
Pro	Asp	Asn	Pro	Cys	Ser	Leu	Lys	Cys	Gln	Ala	Lys	Gly	Thr	Thr	Leu
		35					40					45			
Val	Val	Glu	Leu	Ala	Pro	Lys	Val	Leu	Asp	Gly	Thr	Arg	Cys	Tyr	Thr
	50					55					60				
Glu	Ser	Leu	Asp	Met	Cys	Ile	Ser	Gly	Leu	Cys	Gln	Ile	Val	Gly	Cys
65					70					75					80
Asp	His	Gln	Leu	Gly	Ser	Thr	Val	Lys	Glu	Asp	Asn	Cys	Gly	Val	Cys
				85					90					95	
Asn	Gly	Asp	Gly	Ser	Thr	Cys	Arg	Leu	Val	Arg	Gly	Gln	Tyr	Lys	Ser
			100					105					110		
Gln	Leu	Ser	Ala	Thr	Lys	Ser	Asp	Asp	Thr	Val	Val	Ala	Ile	Pro	Tyr
		115					120					125			
Gly	Ser	Arg	His	Ile	Arg	Leu	Val	Leu	Lys						
	130					135									

<210> 175

129

<211> 292

<212> PRT

<213> Homo sapiens

<400> 175

Ser Val Leu Leu His Cys Glu Ala Ile Gly His Pro Arg Pro Thr Ile
 1 5 10 15

Ser Trp Ala Arg Asn Gly Glu Glu Val Gln Phe Ser Asp Arg Ile Leu
 20 25 30

Leu Gln Pro Asp Asp Ser Leu Gln Ile Leu Ala Pro Val Glu Ala Asp
 35 40 45

Val Gly Phe Tyr Thr Cys Asn Ala Thr Asn Ala Leu Gly Tyr Asp Ser
 50 55 60

Val Ser Ile Ala Val Thr Leu Ala Gly Lys Pro Leu Val Lys Thr Ser
 65 70 75 80

Arg Met Thr Val Ile Asn Thr Glu Lys Pro Ala Val Thr Val Asp Ile
 85 90 95

Gly Ser Thr Ile Lys Thr Val Gln Gly Val Asn Val Thr Ile Asn Cys
 100 105 110

Gln Val Ala Gly Val Pro Glu Ala Glu Val Thr Trp Phe Arg Asn Lys
 115 120 125

Ser Lys Leu Gly Ser Pro His His Leu His Glu Gly Ser Leu Leu Leu
 130 135 140

Thr Asn Val Ser Ser Ser Asp Gln Gly Leu Tyr Ser Cys Arg Ala Ala
 145 150 155 160

Asn Leu His Gly Glu Leu Thr Glu Ser Thr Gln Leu Leu Ile Leu Asp
 165 170 175

Pro Pro Gln Val Pro Thr Gln Leu Glu Asp Ile Arg Ala Leu Leu Ala
 180 185 190

Ala Thr Gly Pro Asn Leu Pro Ser Val Leu Thr Ser Pro Leu Gly Thr
 195 200 205

Gln Leu Val Leu Asp Pro Gly Asn Ser Ala Leu Leu Gly Cys Pro Ile
 210 215 220

Lys Gly His Pro Val Pro Asn Ile Thr Trp Phe His Gly Gly Gln Pro
 225 230 235 240

Ile Val Thr Ala Thr Gly Leu Thr His His Ile Leu Ala Ala Gly Gln
 245 250 255

Ile Leu Gln Val Ala Asn Leu Ser Gly Gly Ser Gln Gly Glu Phe Ser
 260 265 270

Cys Leu Ala Gln Asn Glu Ala Gly Val Leu Met Gln Lys Ala Ser Leu
 275 280 285

Val Ile Gln Asp
 290

<210> 176

<211> 50

<212> PRT

130

<213> Homo sapiens

<400> 176

```

Met Lys Pro Ala Thr Ala Ser Ala Leu Leu Leu Leu Leu Gly Leu
 1           5           10           15
Ala Trp Thr Gln Gly Ser His Gly Trp Gly Ala Asp Ala Ser Ser Leu
           20           25           30
Gln Lys Arg Ala Gly Arg Ala Asp Gln Pro Gly Ala Gly Trp Gln Glu
           35           40           45
Val Ala
 50

```

<210> 177

<211> 67

<212> PRT

<213> Homo sapiens

<400> 177

```

Met Lys Pro Ala Thr Ala Ser Ala Leu Leu Leu Leu Leu Gly Leu
 1           5           10           15
Ala Trp Thr Gln Gly Ser His Gly Trp Gly Ala Asp Ala Ser Ser Leu
           20           25           30
Gln Lys Arg Ala Gly Arg Ala Asp Gln Pro Gly Ala Gly Trp Gln Glu
           35           40           45
Val Ala Ala Val Thr Ser Lys Asn Tyr Asn Tyr Asn Gln His Ala Tyr
           50           55           60
Pro Thr Ala
 65

```

<210> 178

<211> 83

<212> PRT

<213> Homo sapiens

<400> 178

```

Met Lys Pro Ala Thr Ala Ser Ala Leu Leu Leu Leu Leu Gly Leu
 1           5           10           15
Ala Trp Thr Gln Gly Ser His Gly Trp Gly Ala Asp Ala Ser Ser Leu
           20           25           30
Gln Lys Arg Ala Gly Arg Ala Asp Gln Pro Gly Ala Gly Trp Gln Glu
           35           40           45
Val Ala Ala Val Thr Ser Lys Asn Tyr Asn Tyr Asn Gln His Ala Tyr
           50           55           60
Pro Thr Ala Tyr Gly Gly Lys Tyr Ser Val Lys Thr Pro Ala Lys Gly
           65           70           75           80
Gly Val Ser

```

<210> 179

<211> 96

<212> PRT

131

<213> Homo sapiens

<400> 179

```

Met Ala Gly Gly Gly Ser Cys Asn Phe Gln Glu Leu Gln Leu Gln Pro
 1           5           10           15

Ala Cys Val Ser His Cys Leu Trp Trp Glu Val Leu Ser Gln Asp Pro
      20           25           30

Cys Lys Gly Gly Ser Leu Thr Phe Phe Leu Gly Phe Pro Gly Ala Thr
      35           40           45

Trp Pro Ala Ala Val Gly Glu Val Leu Val Gly Asn Phe Leu Gln Pro
      50           55           60

Pro Pro Arg Pro Arg Lys Ala Leu Val Val Arg Glu Leu Leu Pro Leu
      65           70           75           80

Ala Pro Ser Leu Cys Gln Pro Trp Pro Gly Cys His Thr Ser Val Ser
      85           90           95

```

<210> 180

<211> 526

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (37)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (185)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (215)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (216)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (261)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (263)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (311)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE
 <222> (318)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (320)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (510)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (515)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (516)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <220>
 <221> SITE
 <222> (522)
 <223> Xaa equals any of the naturally occurring L-amino acids

 <400> 180
 Arg Pro Arg Leu Gly Ser Ser Ser Gly Ala Ala Ala Glu Asp Ser Ser
 1 5 10 15
 Ala Met Glu Glu Leu Ala Thr Glu Lys Glu Ala Glu Glu Ser His Arg
 20 25 30
 Gln Asp Ser Val Xaa Leu Leu Thr Phe Ile Leu Leu Leu Thr Leu Thr
 35 40 45
 Ile Leu Thr Ile Trp Leu Phe Lys His Arg Arg Val Arg Phe Leu His
 50 55 60
 Glu Thr Gly Leu Ala Met Ile Tyr Gly Leu Ile Val Gly Val Ile Leu
 65 70 75 80
 Arg Tyr Gly Thr Pro Ala Thr Ser Gly Arg Asp Lys Ser Leu Ser Cys
 85 90 95
 Thr Gln Glu Asp Arg Ala Phe Ser Thr Leu Leu Val Asn Val Ser Gly
 100 105 110
 Lys Phe Phe Glu Tyr Thr Leu Lys Gly Glu Ile Ser Pro Gly Lys Ile
 115 120 125
 Asn Ser Val Glu Gln Asn Asp Met Leu Arg Lys Val Thr Phe Asp Pro
 130 135 140
 Glu Val Phe Phe Asn Ile Leu Leu Pro Pro Ile Ile Phe His Ala Gly
 145 150 155 160
 Tyr Ser Leu Lys Lys Arg His Phe Phe Arg Asn Leu Gly Ser Ile Leu
 165 170 175
 Ala Tyr Ala Phe Leu Gly Thr Ala Xaa Ser Cys Phe Ile Ile Gly Asn
 180 185 190

133

Leu Met Tyr Gly Val Val Lys Leu Met Lys Ile Met Gly Gln Leu Ser
 195 200 205
 Asp Lys Phe Tyr Tyr Thr Xaa Xaa Leu Phe Phe Gly Ala Ile Ile Ser
 210 215 220
 Ala Thr Asp Pro Val Thr Val Leu Ala Ile Phe Asn Glu Leu His Ala
 225 230 235 240
 Asp Val Asp Leu Tyr Ala Leu Leu Phe Gly Glu Ser Val Leu Asn Asp
 245 250 255
 Ala Val Ala Ile Xaa Leu Xaa Ser Ser Ile Val Ala Tyr Gln Pro Ala
 260 265 270
 Gly Leu Asn Thr His Ala Phe Asp Ala Ala Ala Phe Phe Lys Ser Val
 275 280 285
 Gly Ile Phe Leu Gly Ile Phe Ser Gly Ser Phe Thr Met Gly Ala Val
 290 295 300
 Thr Gly Val Val Thr Ala Xaa Val Thr Lys Phe Thr Lys Xaa His Xaa
 305 310 315 320
 Phe Pro Leu Leu Glu Thr Ala Leu Phe Phe Leu Met Ser Trp Ser Thr
 325 330 335
 Phe Leu Leu Ala Glu Ala Cys Gly Phe Thr Gly Val Val Ala Val Leu
 340 345 350
 Phe Cys Gly Ile Thr Gln Ala His Tyr Thr Tyr Asn Asn Leu Ser Val
 355 360 365
 Glu Ser Arg Ser Arg Thr Lys Gln Leu Phe Glu Val Leu His Phe Leu
 370 375 380
 Ala Glu Asn Phe Ile Phe Ser Tyr Met Gly Leu Ala Leu Phe Thr Phe
 385 390 395 400
 Gln Lys His Val Phe Ser Pro Ile Phe Ile Ile Gly Ala Phe Val Ala
 405 410 415
 Ile Phe Leu Gly Arg Ala Ala His Ile Tyr Pro Leu Ser Phe Phe Leu
 420 425 430
 Asn Leu Gly Arg Arg His Lys Ile Gly Trp Asn Phe Gln His Met Met
 435 440 445
 Met Phe Ser Gly Leu Arg Gly Ala Met Ala Phe Ala Leu Ala Ile Arg
 450 455 460
 Asp Thr Ala Ser Tyr Ala Arg Gln Met Met Phe Thr Thr Thr Leu Leu
 465 470 475 480
 Ile Val Phe Phe Thr Val Trp Ile Ile Gly Gly Gly Thr Thr Pro Met
 485 490 495
 Leu Ser Trp Leu Asn Ile Arg Val Gly Val Asp Pro Asp Xaa Asp Pro
 500 505 510
 Pro Pro Xaa Xaa Asp Ser Phe Ala Phe Xaa Thr Glu Thr Ala
 515 520 525

<210> 181

<211> 210

134

<212> PRT

<213> Homo sapiens

<400> 181

```

Asn Gly Lys Ile Ser Pro Tyr Tyr Trp Glu Gln Lys Leu Glu Leu His
 1           5           10           15
Arg Gly Gly Gly Arg Ser Arg Thr Ser Gly Ser Pro Gly Leu Gln Glu
          20           25           30
Phe Gly Thr Ser Arg Gly Arg Ala Phe Trp Gly Arg Gly Leu Val Arg
          35           40           45
Leu Thr Leu Glu Gly Phe Ala Ser Ala Ser Glu Thr Val Arg Ile Leu
          50           55           60
Met Thr Met Arg Ser Leu Leu Arg Thr Pro Phe Leu Cys Gly Leu Leu
          65           70           75           80
Trp Ala Phe Cys Ala Pro Gly Ala Arg Ala Glu Glu Pro Ala Ala Ser
          85           90           95
Phe Ser Gln Pro Gly Ser Met Gly Leu Asp Lys Asn Thr Val His Asp
          100           105           110
Gln Glu His Ile Met Glu His Leu Glu Gly Val Ile Asn Lys Pro Glu
          115           120           125
Ala Glu Met Ser Pro Gln Glu Leu Gln Leu His Tyr Phe Lys Met His
          130           135           140
Asp Tyr Asp Gly Asn Asn Leu Leu Asp Gly Leu Glu Leu Ser Thr Ala
          145           150           155           160
Ile Thr His Val His Lys Glu Glu Gly Ser Glu Gln Ala Pro Leu Met
          165           170           175
Ser Glu Asp Glu Leu Ile Asn Ile Ile Asp Gly Val Leu Arg Asp Asp
          180           185           190
Asp Lys Asn Asn Asp Gly Tyr Ile Asp Tyr Ala Glu Phe Ala Lys Ser
          195           200           205
Leu Gln
          210

```

<210> 182

<211> 119

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (118)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 182

```

Met Leu His Asp Met Leu Leu Val Val His Cys Val Leu Ile Gln Ala
 1           5           10           15
His Ala Ala Gly Leu Gly Glu Ala Gly Cys Arg Leu Leu Ser Pro Gly
          20           25           30
Ala Trp Gly Thr Lys Gly Pro Glu Gln Ala Thr Gln Glu Gly Gly Ser
          35           40           45

```

135

Glu Gln Gly Ser His Gly His Gln Tyr Pro Tyr Gly Leu Arg Ser Arg
 50 55 60
 Arg Glu Ala Leu Gln Arg Glu Pro His Gln Pro Pro Ser Pro Lys Arg
 65 70 75 80
 Ser Ser Ser Ala Arg Ala Glu Phe Leu Gln Pro Gly Gly Ser Thr Ser
 85 90 95
 Ser Arg Ala Ala Ala Thr Ala Val Glu Leu Gln Leu Leu Phe Pro Ile
 100 105 110
 Val Arg Gly Asp Phe Xaa Val
 115

<210> 183
 <211> 116
 <212> PRT
 <213> Homo sapiens

<400> 183
 Met Thr Pro Ser Arg Cys Ser Met Ile Cys Ser Trp Ser Cys Thr Val
 1 5 10 15
 Phe Leu Ser Arg Pro Met Leu Pro Gly Trp Glu Lys Leu Ala Ala Gly
 20 25 30
 Ser Ser Ala Leu Ala Pro Gly Ala Gln Lys Ala Gln Ser Arg Pro His
 35 40 45
 Arg Lys Gly Val Leu Ser Arg Asp Leu Met Val Ile Asn Ile Leu Thr
 50 55 60
 Val Ser Glu Ala Asp Ala Lys Pro Ser Asn Val Ser Leu Thr Ser Pro
 65 70 75 80
 Arg Pro Gln Asn Ala Leu Pro Arg Leu Val Pro Asn Ser Cys Ser Pro
 85 90 95
 Gly Asp Pro Leu Val Leu Glu Arg Pro Pro Pro Arg Trp Ser Ser
 100 105 110
 Phe Cys Ser Gln
 115

<210> 184
 <211> 109
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (3)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 184
 Ser Gly Xaa Pro Gly Ser Thr His Ala Ser Ala His Ala Ser Ala Gln
 1 5 10 15
 Leu Pro Ser Gln Asp Val Lys Ile Cys Leu Leu Thr Met Arg Leu Leu
 20 25 30
 Val Leu Ser Ser Leu Leu Cys Ile Leu Leu Leu Cys Phe Ser Ile Phe

136

35 40 45
 Ser Thr Glu Gly Lys Arg Arg Pro Ala Lys Ala Trp Ser Gly Arg Arg
 50 55 60
 Thr Arg Leu Cys Cys His Arg Val Pro Ser Pro Asn Ser Thr Asn Leu
 65 70 75 80
 Lys Gly His His Val Arg Leu Cys Lys Pro Cys Lys Leu Glu Pro Glu
 85 90 95
 Pro Arg Leu Trp Val Val Pro Gly Ala Leu Pro Gln Val
 100 105

<210> 185
 <211> 122
 <212> PRT
 <213> Homo sapiens

<400> 185
 Met Trp Gly Trp Gly Ser Leu Val Ser Ala Arg Gly Gly Trp Gly Val
 1 5 10 15
 Phe Ile Tyr Leu Tyr Met Gly Leu Tyr Ile Val Leu Trp Gly Met Gly
 20 25 30
 Glu Pro Ala Gly Gly Glu Asn Pro Pro Leu Ser Pro His Pro Pro Gly
 35 40 45
 Arg Ala Asn Val Lys Leu Leu Ile Phe Val Leu Tyr Ile Phe Tyr Ile
 50 55 60
 Asn Ile Ser Ile Phe Phe Leu Gln Asn Gln Phe Ile Asn Gly Arg Gly
 65 70 75 80
 Val Trp Gly Gly His Met Glu Leu Pro Leu Trp Gly Gly Pro Leu His
 85 90 95
 Tyr Pro Thr Tyr Arg Pro Phe Pro His Pro Pro Pro His Ser Pro Pro
 100 105 110
 Pro Gly Cys Asp Cys Cys Lys Met Gly Val
 115 120

<210> 186
 <211> 177
 <212> PRT
 <213> Homo sapiens

<400> 186
 Gly Thr Arg Tyr Ala Ala Ala Ser Pro Ala Trp Ala Ala Ala Gln Gln
 1 5 10 15
 Arg Ser His Pro Ala Met Ser Pro Gly Thr Pro Gly Pro Thr Met Gly
 20 25 30
 Arg Ser Gln Gly Ser Pro Met Asp Pro Met Val Met Lys Arg Pro Gln
 35 40 45
 Leu Tyr Gly Met Gly Ser Asn Pro His Ser Gln Pro Gln Gln Ser Ser
 50 55 60
 Pro Tyr Pro Gly Gly Ser Tyr Gly Pro Pro Gly Pro Gln Arg Tyr Pro
 65 70 75 80

137

Ile	Gly	Ile	Gln	Gly	Arg	Thr	Pro	Gly	Ala	Met	Ala	Gly	Met	Gln	Tyr
				85					90					95	
Pro	Gln	Gln	Gln	Met	Pro	Pro	Gln	Tyr	Gly	Gln	Gln	Gly	Val	Ser	Gly
			100					105					110		
Tyr	Cys	Gln	Gln	Gly	Gln	Gln	Pro	Tyr	Tyr	Ser	Gln	Gln	Pro	Gln	Pro
		115					120					125			
Pro	His	Leu	Pro	Pro	Gln	Ala	Gln	Tyr	Leu	Pro	Ser	Gln	Ser	Gln	Gln
	130					135					140				
Arg	Tyr	Gln	Pro	Gln	Gln	Val	Ser	Thr	Val	His	Cys	Pro	Ala	Gly	Pro
145					150					155					160
Val	Phe	Ser	Thr	Lys	Ala	Asp	Pro	Ala	Leu	Asn	His	Leu	Pro	Val	Leu
				165					170					175	

Tyr

```
<210> 187
<211> 132
<212> PRT
<213> Homo sapiens
```

```

<400> 187
Pro Ser Phe Ser Ala Ser Ala Glu Gln Ser Val Pro Arg Arg Phe Leu
  1      5      10      15
Trp Pro Ser Arg Pro Thr Ala Val Ser Asn Trp His Pro Gly Ser Asp
      20      25
Ser Arg Gly His Gly Arg Asn Ala Val Pro Ser Ala Ala Asp Ala Thr
      35      40      45
Ser Val Trp Thr Ala Arg Cys Glu Trp Leu Leu Pro Ala Gly Pro Thr
      50      55      60
Ala Ile Leu Gln Pro Ala Ala Ala Ala Pro Ala Pro Pro Thr Pro Gly
      65      70      75      80
Ala Val Ser Ala Val Pro Val Pro Ala Glu Val Pro Ala Ala Ala Gly
      85      90      95
Glu His Ser Ala Leu Pro Arg Arg Pro Cys Phe Leu His Gln Gly Arg
      100      105
Pro Gly Ser Glu Ser Ser Ser Cys Pro Leu Leu Lys Ile Met Phe Trp
      115      120      125
Trp Lys Lys Asn
      130

```

```
<210> 188
<211> 172
<212> PRT
<213> Homo sapiens
```

<400> 188
Met Ile Gln Ser Arg Val Cys Leu Gly Gly Glu Asn Arg Ala Cys Gly
1 5 10 15

138

Ala Val His Cys Ala His Leu Leu Arg Leu Val Pro Leu Leu Gly Leu
 20 25 30
 Gly Arg Gln Ile Leu Arg Leu Gly Trp Glu Val Arg Gly Leu Arg Leu
 35 40 45
 Leu Ala Val Ile Trp Leu Leu Ala Leu Leu Ala Val Thr Thr His Thr
 50 55 60
 Leu Leu Ser Ile Leu Arg Trp His Leu Leu Leu Arg Val Leu His Ser
 65 70 75 80
 Gly His Gly Pro Gly Ser Pro Thr Leu Asp Ala Asn Trp Ile Pro Leu
 85 90 95
 Trp Ala Trp Arg Ala Ile Gly Thr Ser Trp Val Arg Thr Ala Leu Leu
 100 105 110
 Arg Leu Arg Met Arg Val Thr Ala His Ala Ile Gln Leu Arg Ser Leu
 115 120 125
 His His His Trp Ile His Trp Ala Ala Leu Gly Ser Ala His Gly Arg
 130 135 140
 Ser Gly Gly Ala Gly Ala His Arg Arg Val Thr Pro Leu Leu Arg Gly
 145 150 155 160
 Arg Pro Gly Arg Ala Gly Ser Gly Val Pro Arg Ala
 165 170

<210> 189

<211> 132

<212> PRT

<213> Homo sapiens

<400> 189

Met Thr Leu Phe Gly Leu Phe Val Ser Leu Val Phe Leu Gly Gln Ala
 1 5 10 15
 Phe Thr Ile Met Leu Val Tyr Val Trp Ser Arg Arg Asn Pro Tyr Val
 20 25 30
 Arg Met Asn Phe Phe Gly Leu Leu Asn Phe Gln Ala Pro Phe Leu Pro
 35 40 45
 Trp Val Leu Met Gly Phe Ser Leu Leu Leu Gly Asn Ser Ile Ile Val
 50 55 60
 Asp Leu Leu Gly Ile Ala Val Gly His Ile Tyr Phe Phe Leu Glu Asp
 65 70 75 80
 Val Phe Pro Asn Gln Pro Gly Gly Ile Arg Ile Leu Lys Thr Pro Ser
 85 90 95
 Ile Leu Lys Ala Ile Phe Asp Thr Pro Asp Glu Asp Pro Asn Tyr Asn
 100 105 110
 Pro Leu Pro Glu Glu Arg Pro Gly Gly Phe Ala Trp Gly Glu Gly Gln
 115 120 125
 Arg Leu Gly Gly
 130

<210> 190

<211> 310

<212> PRT

<213> Homo sapiens

<400> 190

Cys Thr Cys Lys Ile Ile Gly Gly Pro Gly Ser Arg Gly Cys Ala Ala
 1 5 10 15
 Ser Ser Ser Trp Ala Ser Ser Ser Arg Pro Ser Pro Ser Leu Pro Ser
 20 25 30
 Ala Pro Ser Ser Cys Trp Pro Ser Pro Gly Ile Arg Ala Ser Gln Thr
 35 40 45
 Pro Pro Ala Thr Thr Ser Pro Ala Ser Gly Ala Ser Phe Pro Ser Ser
 50 55 60
 Gly Pro Ser Cys Ser Ala Ser Met Pro Thr Ala Thr Gly Leu Thr Leu
 65 70 75 80
 Leu Thr Ser Ala Ser Ser Ala Ile Ser Asp Pro Gly Gly Glu Val Ser
 85 90 95
 Ala Pro Trp Gly Gly Leu Arg Thr Trp Thr Gln Pro Leu Arg Cys Trp
 100 105 110
 Glu Arg Leu Leu Pro Pro Pro Gly Asp Pro Arg Thr Val Ala Glu Asn
 115 120 125
 Thr Gln Gln Asp Glu Cys Gly Leu Pro Gly Ser Cys Pro Ala Arg Pro
 130 135 140
 Leu Ser Arg Lys Pro Glu Cys Gly Arg Glu Gly Ile Leu Pro Cys Cys
 145 150 155 160
 Ser Ser Ser Ala Trp Pro Glu Gly Ser Phe Arg Pro Phe Gln Met Asn
 165 170 175
 Leu Phe Ser Phe Leu Ser Phe Phe Phe Leu Phe Phe Phe Phe Leu Arg
 180 185 190
 Trp Ser Leu Thr Leu Ser Pro Arg Leu Glu Cys Ser Ser Ala Ile Ser
 195 200 205
 Ala His Cys Asn Leu Arg Leu Pro Gly Ser Ser Asn Ser Pro Ala Leu
 210 215 220
 Ala Ser Gln Val Ala Gly Ile Thr Gly Ile Cys His His Ala Arg Gln
 225 230 235 240
 Ile Phe Val Phe Leu Val Glu Thr Gly Phe Cys His Val Gly Gln Ala
 245 250 255
 Gly Leu Glu Leu Leu Ile Ser Gly Asp Ser Pro Ala Ser Ala Phe Gln
 260 265 270
 Ser Ala Gly Ile Ile Gly Val Ser His Arg Ala Arg Pro Gly Ser Val
 275 280 285
 Phe Leu Ala Arg Ser Glu Glu Ser Leu Tyr Leu Arg Pro Gly Gln Gln
 290 295 300
 Ser Gln Glu Val Lys Val
 305 310

140

<210> 191
 <211> 160
 <212> PRT
 <213> Homo sapiens

<400> 191
 Met Arg Pro Gly Pro Met Leu Gln Ala Arg Val Ser Ile Pro Ala Ala
 1 5 10 15
 Leu Gly Thr Leu Phe Pro Arg Pro Gly Trp Ala Pro Gly Glu Val Ser
 20 25 30
 Ser Glu Ile Ser Ser Arg Asp Leu Leu Asn Pro His Pro Ser Thr Pro
 35 40 45
 Ser Cys Cys Ser Gln Ser Trp Ser Pro Met Ser Val Leu Glu Pro Asp
 50 55 60
 Ser Arg Gly Pro Pro Pro Ile Ser Leu Thr His Thr Gly Ile His Thr
 65 70 75 80
 Pro Gln Lys Thr Ser Gln Met Arg Pro Asp Ser Gly Ser Arg Gly Met
 85 90 95
 Cys Phe Cys Pro Cys Lys Gly Phe Gly Glu Gly Gly Asn Ile Val Glu
 100 105 110
 Ala Gly Lys Ser Pro Gln Thr Cys Ala His Ala Pro Pro Ala Leu Arg
 115 120 125
 Phe His Ser Ala Phe Ser Glu Gly Pro Cys Cys Thr Gln Thr Thr Gly
 130 135 140
 Gln Glu Arg Pro Cys Leu Pro Leu Gln Pro Leu Ser Leu Pro Phe Asn
 145 150 155 160

<210> 192
 <211> 161
 <212> PRT
 <213> Homo sapiens

<400> 192
 His Ala Ser Ala Leu Ala Leu Gly Pro Pro Gly Ala Ala Ala Pro Trp
 1 5 10 15
 Pro Arg Pro Gly Cys Ser Ser Ala Ser Ala Pro Pro Thr Pro Ala Ser
 20 25 30
 Ala Pro Trp Pro Ala Ser Pro Ser Ser Ser Gly Arg Trp Ser Thr
 35 40 45
 Asp Ser Arg Gly Pro Arg Leu Met Gly Gly Leu Ala Gly Val Leu Ala
 50 55 60
 Leu Trp Val Leu Val Thr His Val Met Tyr Met Gln Asp Tyr Trp Arg
 65 70 75 80
 Thr Trp Leu Lys Gly Leu Arg Gly Phe Phe Phe Val Gly Val Leu Phe
 85 90 95
 Ser Ala Val Ser Ile Ala Ala Phe Cys Thr Phe Leu Val Leu Ala Ile
 100 105 110

141

Thr Arg His Gln Ser Leu Thr Asp Pro Thr Ser Tyr Tyr Leu Ser Ser
 115 120 125
 Val Trp Ser Phe Ile Ser Phe Lys Trp Ala Phe Leu Leu Ser Leu Tyr
 130 135 140
 Ala His Arg Tyr Arg Ala Asp Phe Ala Asp Ile Ser Ile Leu Ser Asp
 145 150 155 160
 Phe

<210> 193
 <211> 239
 <212> PRT
 <213> Homo sapiens

<400> 193
 Met Pro Thr Ala Thr Gly Leu Thr Leu Leu Thr Ser Ala Ser Ser Ala
 1 5 10 15
 Ile Ser Asp Pro Gly Gly Glu Val Ser Ala Pro Trp Gly Gly Leu Arg
 20 25 30
 Thr Trp Thr Gln Pro Leu Arg Cys Trp Glu Arg Leu Leu Pro Pro Pro
 35 40 45
 Gly Asp Pro Arg Thr Val Ala Glu Asn Thr Gln Gln Asp Glu Cys Gly
 50 55 60
 Leu Pro Gly Ser Cys Pro Ala Arg Pro Leu Ser Arg Lys Pro Glu Cys
 65 70 75 80
 Gly Arg Glu Gly Ile Leu Pro Cys Cys Ser Ser Ser Ala Trp Pro Glu
 85 90 95
 Gly Ser Phe Arg Pro Phe Gln Met Asn Leu Phe Ser Phe Leu Ser Phe
 100 105 110
 Phe Phe Leu Phe Phe Phe Phe Leu Arg Trp Ser Leu Thr Leu Ser Pro
 115 120 125
 Arg Leu Glu Cys Ser Ser Ala Ile Ser Ala His Cys Asn Leu Arg Leu
 130 135 140
 Pro Gly Ser Ser Asn Ser Pro Ala Leu Ala Ser Gln Val Ala Gly Ile
 145 150 155 160
 Thr Gly Ile Cys His His Ala Arg Gln Ile Phe Val Phe Leu Val Glu
 165 170 175
 Thr Gly Phe Cys His Val Gly Gln Ala Gly Leu Glu Leu Leu Ile Ser
 180 185 190
 Gly Asp Ser Pro Ala Ser Ala Phe Gln Ser Ala Gly Ile Ile Gly Val
 195 200 205
 Ser His Arg Ala Arg Pro Gly Ser Val Phe Leu Ala Arg Ser Glu Glu
 210 215 220
 Ser Leu Tyr Leu Arg Pro Gly Gln Gln Ser Gln Glu Val Lys Val
 225 230 235

142

<210> 194
 <211> 135
 <212> PRT
 <213> Homo sapiens

<400> 194
 Met Ala Pro Ser Arg Leu Gln Leu Gly Leu Arg Ala Ala Tyr Ser Gly
 1 5 10 15
 Ile Ser Ser Val Ala Gly Phe Ser Ile Phe Leu Val Trp Thr Val Val
 20 25 30
 Tyr Arg Gln Pro Gly Thr Ala Ala His Gly Arg Ala Arg Arg Gly Ala
 35 40 45
 Gly Thr Val Gly Pro Gly Asp Ala Arg Asn Val His Ala Arg Leu Leu
 50 55 60
 Glu Asp Leu Ala Gln Gly Ala Ala Arg Leu Leu Leu Arg Gly Arg Pro
 65 70 75 80
 Leu Leu Gly Arg Leu His Arg Cys Leu Leu His Leu Pro Arg Ala Gly
 85 90 95
 His His Pro Ala Ser Glu Pro His Arg Pro His Gln Leu Leu Pro Leu
 100 105 110
 Gln Arg Leu Glu Leu His Phe Leu Gln Val Gly Leu Pro Ala Gln Pro
 115 120 125
 Leu Cys Pro Pro Leu Pro Gly
 130 135

<210> 195
 <211> 326
 <212> PRT
 <213> Homo sapiens

<400> 195
 Pro Arg Val Arg Gly Lys Gly Lys Lys Ile Phe Ile His Met His Glu
 1 5 10 15
 Ile Ile Gln Ile Asp Gly His Ile Tyr Gln Cys Leu Glu Cys Lys Gln
 20 25 30
 Asn Phe Cys Glu Asn Leu Ala Leu Ile Met Cys Gln Arg Thr His Thr
 35 40 45
 Gly Glu Lys Pro Tyr Lys Cys Asp Met Cys Glu Lys Thr Phe Val Gln
 50 55 60
 Ser Ser Asp Leu Thr Ser His Gln Arg Ile His Asn Tyr Glu Lys Pro
 65 70 75 80
 Tyr Lys Cys Ser Lys Cys Glu Lys Ser Phe Trp His His Leu Ala Leu
 85 90 95
 Ser Gly His Gln Arg Thr His Ala Gly Lys Lys Phe Tyr Thr Cys Asp
 100 105 110
 Ile Cys Gly Lys Asn Phe Gly Gln Ser Ser Asp Leu Leu Val His Gln
 115 120 125
 Arg Ser His Thr Gly Glu Lys Pro Tyr Leu Cys Ser Glu Cys Asp Lys
 130 135 140

143

Cys Phe Ser Arg Ser Thr Asn Leu Ile Arg His Arg Arg Thr His Thr
 145 150 155 160
 Gly Glu Lys Pro Phe Lys Cys Leu Asp Val Lys Lys Leu Leu Val Gly
 165 170 175
 Asn Gln Ile Leu Leu Ala Thr Arg Glu Leu Thr Leu Gly Lys Gly Pro
 180 185 190
 Thr Asn Val Ile Ser Val Arg Lys Val Thr Asp Thr Val Gln Pro Ser
 195 200 205
 Leu Tyr Ile Lys Glu Phe Ile Leu Gly Arg Ser Pro Ile Ser Val Glu
 210 215 220
 Pro Val Lys Asn Ala Leu Ala Arg Asn Gln Thr Leu Ser Val His Gln
 225 230 235 240
 Arg Val His Thr Gly Glu Lys Pro Tyr Lys Cys Leu Glu Cys Met Arg
 245 250 255
 Ser Phe Thr Arg Ser Ala Asn Leu Ile Arg His Gln Ala Thr His Thr
 260 265 270
 His Thr Phe Lys Cys Leu Glu Tyr Glu Lys Ser Phe Asn Cys Ser Ser
 275 280 285
 Arg Ser Asn Cys Thr Ser Val Glu Phe Thr Trp Lys Arg Thr Pro Thr
 290 295 300
 Ser Val Val Trp Arg Leu Glu Ser Gly Phe Leu Leu Arg Asn Gly Leu
 305 310 315 320
 Cys Cys Pro Thr Arg Lys
 325

<210> 196
 <211> 313
 <212> PRT
 <213> Homo sapiens

<400> 196
 Met His Glu Ile Ile Gln Ile Asp Gly His Ile Tyr Gln Cys Leu Glu
 1 5 10 15
 Cys Lys Gln Asn Phe Cys Glu Asn Leu Ala Leu Ile Met Cys Gln Arg
 20 25 30
 Thr His Thr Gly Glu Lys Pro Tyr Lys Cys Asp Met Cys Glu Lys Thr
 35 40 45
 Phe Val Gln Ser Ser Asp Leu Thr Ser His Gln Arg Ile His Asn Tyr
 50 55 60
 Glu Lys Pro Tyr Lys Cys Ser Lys Cys Glu Lys Ser Phe Trp His His
 65 70 75 80
 Leu Ala Leu Ser Gly His Gln Arg Thr His Ala Gly Lys Lys Phe Tyr
 85 90 95
 Thr Cys Asp Ile Cys Gly Lys Asn Phe Gly Gln Ser Ser Asp Leu Leu
 100 105 110
 Val His Gln Arg Ser His Thr Gly Glu Lys Pro Tyr Leu Cys Ser Glu

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115					120					125					
Cys	Asp	Lys	Cys	Phe	Ser	Arg	Ser	Thr	Asn	Leu	Ile	Arg	His	Arg	Arg
130						135					140				
Thr	His	Thr	Gly	Glu	Lys	Pro	Phe	Lys	Cys	Leu	Glu	Cys	Glu	Lys	Ala
145					150					155					160
Phe	Ser	Gly	Lys	Ser	Asp	Leu	Ile	Ser	His	Gln	Arg	Thr	His	Thr	Gly
			165						170					175	
Glu	Arg	Pro	Tyr	Lys	Cys	Asn	Lys	Cys	Glu	Lys	Ser	Tyr	Arg	His	Arg
			180					185					190		
Ser	Ala	Phe	Ile	Val	His	Lys	Arg	Val	His	Thr	Gly	Glu	Lys	Pro	Tyr
		195					200					205			
Lys	Cys	Gly	Ala	Cys	Glu	Lys	Cys	Phe	Gly	Gln	Lys	Ser	Asp	Leu	Ile
	210					215					220				
Val	His	Gln	Arg	Val	His	Thr	Gly	Glu	Lys	Pro	Tyr	Lys	Cys	Leu	Glu
225					230					235					240
Cys	Met	Arg	Ser	Phe	Thr	Arg	Ser	Ala	Asn	Leu	Ile	Arg	His	Gln	Ala
				245					250					255	
Thr	His	Thr	His	Thr	Phe	Lys	Cys	Leu	Glu	Tyr	Glu	Lys	Ser	Phe	Asn
			260					265					270		
Cys	Ser	Ser	Arg	Ser	Asn	Cys	Thr	Ser	Val	Glu	Phe	Thr	Trp	Lys	Lys
		275					280					285			
Thr	Pro	Thr	Ser	Val	Val	Trp	Arg	Leu	Glu	Ser	Gly	Phe	Leu	Leu	Arg
	290					295					300				
Asn	Gly	Leu	Cys	Cys	Pro	Thr	Arg	Lys							
305					310										

<210> 197
 <211> 60
 <212> PRT
 <213> Homo sapiens

<400> 197
 Gly Thr Arg Glu Arg Gly Leu Arg Thr Pro Gln Met Val Leu Val Phe
 1 5 10 15
 Ala Tyr Leu Cys Val Leu Leu Ile Val Cys Trp Val Thr Ser Lys Thr
 20 25 30
 Ser Leu Ala Leu Lys Tyr Thr Val Tyr Lys Asn Phe Lys Arg Leu Ile
 35 40 45
 Trp Asn Lys Ser Ile Leu Ile Ile Thr Leu Thr Pro
 50 55 60

<210> 198
 <211> 142
 <212> PRT
 <213> Homo sapiens

<400> 198
 Met His Gln Leu Leu Gln Leu Gln Arg Gln Glu Pro Cys Arg Leu Leu
 1 5 10 15

145

Ser Pro Ser Pro Gln Pro Gly Leu His His Leu Cys Phe Gln Gln Ile
 20 25 30
 Glu Leu Leu Leu Leu Leu Leu His Leu Gln Trp Gly Leu Gly Leu Leu
 35 40 45
 Arg Gln Leu His His Lys Arg Leu Ala Gln Leu Leu Leu His Arg Arg
 50 55 60
 Arg Asp His Pro Ile Pro Pro Ile Gln Asp Ile Leu Gly Ile Ala Lys
 65 70 75 80
 Cys Pro Cys Pro Trp Ala Ile Ile Leu Met Arg Met Ala Ser Ile Ile
 85 90 95
 Cys His Ile His Gln Cys Ile Thr Arg Val Leu Asp Arg Leu Arg Thr
 100 105 110
 Arg Asp Pro Ser Ser Leu His Thr Pro Ser Leu Ser Pro His Ser Ser
 115 120 125
 Leu Thr Ile His Ser Ser Asn Met Ser Ala Gln Gln Leu Ser
 130 135 140

<210> 199
 <211> 921
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (247)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (362)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (603)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 199
 Val Gly Ala Pro Gly Lys Leu Pro Asp Pro Glu Arg Arg Arg Ser Ala
 1 5 10 15
 Ser Leu Ser Ala Ser Gln Ser Ala Ser Pro Pro Ala Gln Tyr Leu Ser
 20 25 30
 Leu Leu Gly Pro Arg Lys Leu Ser Ala Val Cys Leu Ala Arg Thr Ala
 35 40 45
 Ala Glu Ala Leu Ile Met Ala Thr Phe Ile Ser Val Gln Leu Lys Lys
 50 55 60
 Thr Ser Glu Val Asp Leu Ala Lys Pro Leu Val Lys Phe Ile Gln Gln
 65 70 75 80
 Thr Tyr Pro Ser Gly Gly Glu Glu Gln Ala Gln Tyr Cys Arg Ala Ala
 85 90 95
 Glu Glu Leu Ser Lys Leu Arg Arg Ala Ala Val Gly Arg Pro Leu Asp

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100					105					110					
Lys	His	Glu	Gly	Ala	Leu	Glu	Thr	Leu	Leu	Arg	Tyr	Tyr	Asp	Gln	Ile
		115					120					125			
Cys	Ser	Ile	Glu	Pro	Lys	Phe	Pro	Phe	Ser	Glu	Asn	Gln	Ile	Cys	Leu
	130					135					140				
Thr	Phe	Thr	Trp	Lys	Asp	Ala	Phe	Asp	Lys	Gly	Ser	Leu	Phe	Gly	Gly
145					150					155					160
Ser	Val	Lys	Leu	Ala	Leu	Ala	Ser	Leu	Gly	Tyr	Glu	Lys	Ser	Cys	Val
			165						170					175	
Leu	Phe	Asn	Cys	Ala	Ala	Leu	Ala	Ser	Gln	Ile	Ala	Ala	Glu	Gln	Asn
			180					185					190		
Leu	Asp	Asn	Asp	Glu	Gly	Leu	Lys	Ile	Ala	Ala	Lys	His	Tyr	Gln	Phe
	195						200					205			
Ala	Ser	Gly	Ala	Phe	Leu	His	Ile	Lys	Glu	Thr	Val	Leu	Ser	Ala	Leu
	210					215					220				
Ser	Arg	Glu	Pro	Thr	Val	Asp	Ile	Ser	Pro	Asp	Thr	Val	Gly	Thr	Leu
225					230					235					240
Ser	Leu	Ile	Met	Leu	Ala	Xaa	Ala	Gln	Glu	Val	Phe	Phe	Leu	Lys	Ala
			245						250					255	
Thr	Arg	Asp	Lys	Met	Lys	Asp	Ala	Ile	Ile	Ala	Lys	Leu	Ala	Asn	Gln
			260					265					270		
Ala	Ala	Asp	Tyr	Phe	Gly	Asp	Ala	Phe	Lys	Gln	Cys	Gln	Tyr	Lys	Asp
		275					280					285			
Thr	Leu	Pro	Lys	Glu	Val	Phe	Pro	Val	Leu	Ala	Ala	Lys	His	Cys	Ile
	290					295					300				
Met	Gln	Ala	Asn	Ala	Glu	Tyr	His	Gln	Ser	Ile	Leu	Ala	Lys	Gln	Gln
305					310					315					320
Lys	Lys	Phe	Gly	Glu	Glu	Ile	Ala	Arg	Leu	Gln	His	Ala	Ala	Glu	Leu
			325						330					335	
Ile	Lys	Thr	Val	Ala	Ser	Arg	Tyr	Asp	Glu	Tyr	Val	Asn	Val	Lys	Asp
		340						345					350		
Phe	Ser	Asp	Lys	Ile	Asn	Arg	Ala	Leu	Xaa	Ala	Ala	Lys	Lys	Asp	Asn
		355					360					365			
Asp	Phe	Ile	Tyr	His	Asp	Arg	Val	Pro	Asp	Leu	Lys	Asp	Leu	Asp	Pro
	370					375					380				
Ile	Gly	Lys	Ala	Thr	Leu	Val	Lys	Ser	Thr	Pro	Val	Asn	Val	Pro	Ile
385					390					395					400
Ser	Gln	Lys	Phe	Thr	Asp	Leu	Phe	Glu	Lys	Met	Val	Pro	Val	Ser	Val
			405					410						415	
Gln	Gln	Ser	Leu	Ala	Ala	Tyr	Asn	Gln	Arg	Lys	Ala	Asp	Leu	Val	Asn
			420					425					430		
Arg	Ser	Ile	Ala	Gln	Met	Arg	Glu	Ala	Thr	Thr	Leu	Ala	Asn	Gly	Val
		435					440					445			
Leu	Ala	Ser	Leu	Asn	Leu	Pro	Ala	Ala	Ile	Glu	Asp	Val	Ser	Gly	Asp

450					455					460					
Thr	Val	Pro	Gln	Ser	Ile	Leu	Thr	Lys	Ser	Arg	Ser	Val	Ile	Glu	Gln
465					470					475					480
Gly	Gly	Ile	Gln	Thr	Val	Asp	Gln	Leu	Ile	Lys	Glu	Leu	Pro	Glu	Leu
				485					490					495	
Leu	Gln	Arg	Asn	Arg	Glu	Ile	Leu	Asp	Glu	Ser	Leu	Arg	Leu	Leu	Asp
			500					505					510		
Glu	Glu	Glu	Ala	Thr	Asp	Asn	Asp	Leu	Arg	Ala	Lys	Phe	Lys	Glu	Arg
			515				520					525			
Trp	Gln	Arg	Thr	Pro	Ser	Asn	Glu	Leu	Tyr	Lys	Pro	Leu	Arg	Ala	Glu
	530					535					540				
Gly	Thr	Asn	Phe	Arg	Thr	Val	Leu	Asp	Lys	Ala	Val	Gln	Ala	Asp	Gly
545					550					555					560
Gln	Val	Lys	Glu	Cys	Tyr	Gln	Ser	His	Arg	Asp	Thr	Ile	Val	Leu	Leu
				565					570					575	
Cys	Lys	Pro	Glu	Pro	Glu	Leu	Asn	Ala	Ala	Ile	Pro	Ser	Ala	Asn	Pro
			580					585					590		
Ala	Lys	Thr	Met	Gln	Gly	Ser	Glu	Val	Val	Xaa	Val	Leu	Lys	Ser	Leu
		595					600					605			
Leu	Ser	Asn	Leu	Asp	Glu	Val	Lys	Lys	Glu	Arg	Glu	Gly	Leu	Glu	Asn
	610					615					620				
Asp	Leu	Lys	Ser	Val	Asn	Phe	Asp	Met	Thr	Ser	Lys	Phe	Leu	Thr	Ala
625					630					635					640
Leu	Ala	Gln	Asp	Gly	Val	Ile	Asn	Glu	Glu	Ala	Leu	Ser	Val	Thr	Glu
				645					650					655	
Leu	Asp	Arg	Val	Tyr	Gly	Gly	Leu	Thr	Thr	Lys	Val	Gln	Glu	Ser	Leu
			660					665					670		
Lys	Lys	Gln	Glu	Gly	Leu	Leu	Lys	Asn	Ile	Gln	Val	Ser	His	Gln	Glu
		675					680					685			
Phe	Ser	Lys	Met	Lys	Gln	Ser	Asn	Asn	Glu	Ala	Asn	Leu	Arg	Glu	Glu
	690					695					700				
Val	Leu	Lys	Asn	Leu	Ala	Thr	Ala	Tyr	Asp	Asn	Phe	Val	Glu	Leu	Val
705					710					715					720
Ala	Asn	Leu	Lys	Glu	Gly	Thr	Lys	Phe	Tyr	Asn	Glu	Leu	Thr	Glu	Ile
				725					730					735	
Leu	Val	Arg	Phe	Gln	Asn	Lys	Cys	Ser	Asp	Ile	Val	Phe	Ala	Arg	Lys
			740					745					750		
Thr	Glu	Arg	Asp	Glu	Leu	Leu	Lys	Asp	Leu	Gln	Gln	Ser	Ile	Ala	Arg
		755					760					765			
Glu	Pro	Ser	Ala	Pro	Ser	Ile	Pro	Thr	Pro	Ala	Tyr	Gln	Ser	Leu	Pro
	770					775					780				
Ala	Gly	Gly	His	Ala	Pro	Thr	Pro	Pro	Thr	Pro	Ala	Pro	Arg	Thr	Met
785					790					795					800
Pro	Pro	Thr	Lys	Pro	Gln	Pro	Pro	Ala	Arg	Pro	Pro	Pro	Pro	Val	Leu

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805					810					815					
Pro	Ala	Asn	Arg	Ala	Pro	Ser	Ala	Thr	Ala	Pro	Ser	Pro	Val	Gly	Ala
			820					825					830		
Gly	Thr	Ala	Ala	Pro	Ala	Pro	Ser	Gln	Thr	Pro	Gly	Ser	Ala	Pro	Pro
		835					840					845			
Pro	Gln	Ala	Gln	Gly	Pro	Pro	Tyr	Pro	Thr	Tyr	Pro	Gly	Tyr	Pro	Gly
	850					855					860				
Tyr	Cys	Gln	Met	Pro	Met	Pro	Met	Gly	Tyr	Asn	Pro	Tyr	Ala	Tyr	Gly
865				870						875					880
Gln	Tyr	Asn	Met	Pro	Tyr	Pro	Pro	Val	Tyr	His	Gln	Ser	Pro	Gly	Gln
			885						890					895	
Ala	Pro	Tyr	Pro	Gly	Pro	Gln	Gln	Pro	Ser	Tyr	Pro	Phe	Pro	Gln	Pro
			900					905					910		
Pro	Gln	Gln	Ser	Tyr	Tyr	Pro	Gln	Gln							
	915						920								

<210> 200
 <211> 91
 <212> PRT
 <213> Homo sapiens

<400> 200
 Val Ala Val Ser Asn Asn Ser Gln Ala Gln Val Thr Trp Asn Leu Gly
 1 5 10 15
 Ala Ala Leu Cys Ser Gly Ser Gln Trp Leu Pro Glu Arg Ala Ser Ala
 20 25 30
 Lys Cys Glu Met Arg Gly His Ile Thr Thr Leu Leu Thr Thr Ser Phe
 35 40 45
 Leu Val Phe Gly Leu His Ile Ile Phe Phe Leu Asn Ile Ser Cys Phe
 50 55 60
 Asn Phe Arg Val Phe Ile Leu Phe Glu Thr Arg Pro Glu Asp Ser Arg
 65 70 75 80
 Leu Tyr Arg Glu Arg Pro Val Leu Pro Arg Tyr
 85 90

<210> 201
 <211> 123
 <212> PRT
 <213> Homo sapiens

<400> 201
 Ala Ile Arg Pro Thr Glu Glu Gly Gly Leu His Val His Met Glu Phe
 1 5 10 15
 Pro Gly Ala Asp Gly Cys Asn Gln Val Asp Ala Glu Tyr Leu Lys Val
 20 25 30
 Gly Ser Glu Gly His Phe Arg Val Pro Ala Leu Gly Tyr Leu Asp Val
 35 40 45
 Arg Ile Val Asp Thr Asp Tyr Ser Ser Phe Ala Val Leu Tyr Ile Tyr
 50 55 60

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Lys Glu Leu Glu Gly Ala Leu Ser Thr Met Val Gln Leu Tyr Ser Arg
 65 70 75 80
 Thr Gln Asp Val Ser Pro Gln Ala Leu Lys Ala Phe Gln Asp Phe Tyr
 85 90 95
 Pro Thr Leu Gly Leu Pro Glu Asp Met Met Val Met Leu Pro Gln Ser
 100 105 110
 Asp Ala Cys Asn Pro Glu Ser Lys Glu Ala Pro
 115 120

<210> 202
 <211> 183
 <212> PRT
 <213> Homo sapiens

<400> 202
 Met Lys Gly Leu Val Leu Ser Phe Ala Leu Val Ala Leu Ser Ala Leu
 1 5 10 15
 Cys Val Tyr Gly Asp Val Pro Ile Gln Pro Asp Phe Gln Glu Asp Lys
 20 25 30
 Ile Leu Gly Lys Trp Tyr Gly Ile Gly Leu Ala Ser Asn Ser Asn Trp
 35 40 45
 Phe Gln Ser Lys Lys Gln Gln Leu Lys Met Cys Thr Thr Val Ile Thr
 50 55 60
 Pro Thr Ala Asp Gly Asn Leu Asp Val Val Ala Thr Phe Pro Lys Leu
 65 70 75 80
 Asp Arg Cys Glu Lys Lys Ser Met Thr Tyr Ile Lys Thr Glu Gln Pro
 85 90 95
 Gly Arg Phe Leu Ser Lys Ser Pro Arg Tyr Gly Ser Asp His Val Ile
 100 105 110
 Arg Val Val Glu Ser Asn Tyr Asp Glu Tyr Thr Leu Met His Thr Ile
 115 120 125
 Lys Thr Lys Gly Asn Glu Val Asn Thr Ile Val Ser Leu Phe Gly Arg
 130 135 140
 Arg Lys Thr Leu Ser Pro Glu Leu Leu Asp Lys Phe Gln Gln Phe Ala
 145 150 155 160
 Lys Glu Gln Gly Leu Thr Asp Asp Asn Ile Leu Ile Leu Pro Gln Thr
 165 170 175
 Asp Ser Cys Met Ser Glu Val
 180

<210> 203
 <211> 184
 <212> PRT
 <213> Homo sapiens

<400> 203
 Met Met Arg Ile Leu Leu Ala Leu Ser Leu Gly Val Ala Cys Cys Ser
 1 5 10 15

150

Leu Trp Val Gly Ala Glu Val Gln Val Gln Pro Asp Phe Gln Lys Glu
 20 25 30
 Lys Val Leu Gly Lys Trp Tyr Gly Ile Gly Leu Ala Ser Asn Ser Asn
 35 40 45
 Trp Phe Lys Asp Arg Lys Ser His Met Lys Met Cys Thr Thr Ile Ile
 50 55 60
 Thr Pro Thr Ala Asp Gly Asn Val Glu Val Thr Ala Thr Tyr Pro Lys
 65 70 75 80
 Met Asp Arg Cys Glu Thr Lys Ser Met Thr Tyr Phe Lys Thr Glu Gln
 85 90 95
 Leu Gly Arg Phe Arg Ala Lys Ser Pro Arg Tyr Gly Ser Glu His Asp
 100 105 110
 Met Arg Val Val Glu Thr Asn Tyr Asp Glu Tyr Ile Leu Met Tyr Thr
 115 120 125
 Val Lys Thr Lys Gly Ser Glu Thr Asn Gln Ile Val Ser Leu Phe Gly
 130 135 140
 Arg Asp Lys Asp Leu Arg Pro Glu Leu Leu Asp Lys Phe Gln Asn Phe
 145 150 155 160
 Ala Lys Ser Gln Gly Leu Ala Asp Asp Asn Ile Ile Ile Leu Pro His
 165 170 175
 Thr Asp Gln Cys Met Thr Glu Ala
 180

<210> 204
 <211> 184
 <212> PRT
 <213> Homo sapiens

<400> 204
 Met Met Arg Ile Leu Leu Ala Leu Ser Leu Gly Val Ala Cys Cys Ser
 1 5 10 15
 Leu Trp Val Gly Ala Glu Val Gln Val Gln Pro Asp Phe Gln Lys Glu
 20 25 30
 Lys Val Leu Gly Lys Trp Tyr Gly Ile Gly Leu Ala Ser Asn Ser Asn
 35 40 45
 Trp Phe Lys Asp Arg Lys Ser His Met Lys Met Cys Thr Thr Ile Ile
 50 55 60
 Thr Pro Thr Ala Asp Gly Asn Leu Glu Val Thr Ala Thr Tyr Pro Lys
 65 70 75 80
 Met Asp Arg Cys Glu Thr Lys Ser Met Thr Tyr Phe Lys Thr Glu Gln
 85 90 95
 Leu Gly Gly Phe Arg Ala Lys Ser Pro Arg Tyr Gly Ser Glu His Asp
 100 105 110
 Met Arg Val Val Glu Thr Asn Tyr Asp Glu Tyr Ile Leu Met Tyr Thr
 115 120 125
 Val Lys Thr Lys Gly Ser Glu Thr Asn Gln Ile Val Ser Leu Phe Gly
 130 135 140

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Arg Asp Lys Asp Leu Arg Pro Glu Leu Leu Asp Lys Phe Gln Asn Phe
 145 150 155 160
 Ala Lys Ser Gln Gly Leu Ala Asp Asp Asn Ile Ile Ile Leu Pro His
 165 170 175
 Thr Asp Gln Cys Met Thr Glu Ala
 180

<210> 205
 <211> 224
 <212> PRT
 <213> Homo sapiens

<400> 205
 Pro Arg Val Arg Asn Arg Lys Arg Arg Leu Ser Ala Val Pro Ala Gly
 1 5 10 15
 Gly Gly Glu Ala Ala Val Gly Ser Leu Gly Cys Val Ser Pro Val Met
 20 25 30
 Glu Pro Gly Pro Thr Ala Ala Gln Arg Arg Cys Ser Leu Pro Pro Trp
 35 40 45
 Leu Pro Leu Gly Leu Leu Leu Trp Ser Gly Leu Ala Leu Gly Ala Leu
 50 55 60
 Pro Phe Gly Ser Ser Pro His Arg Val Phe His Asp Leu Leu Ser Glu
 65 70 75 80
 Gln Gln Leu Leu Glu Val Glu Asp Leu Ser Leu Ser Leu Leu Gln Gly
 85 90 95
 Gly Gly Leu Gly Pro Leu Ser Leu Pro Pro Asp Leu Pro Asp Leu Asp
 100 105 110
 Pro Glu Cys Arg Glu Leu Leu Leu Asp Phe Ala Asn Ser Ser Ala Glu
 115 120 125
 Leu Thr Gly Cys Leu Val Arg Ser Ala Arg Pro Val Arg Leu Cys Gln
 130 135 140
 Thr Cys Tyr Pro Leu Phe Gln Gln Val Val Ser Lys Met Asp Asn Ile
 145 150 155 160
 Ser Arg Ala Ala Gly Asn Thr Ser Glu Ser Gln Ser Cys Ala Arg Ser
 165 170 175
 Leu Leu Met Ala Asp Arg Met Gln Ile Val Val Ile Leu Ser Glu Phe
 180 185 190
 Phe Asn Thr Thr Trp Gln Glu Ala Asn Cys Ala Asn Cys Leu Thr Asn
 195 200 205
 Asn Ser Glu Glu Leu Ser Asn Ser Thr Val Tyr Phe Leu Lys Ser Ile
 210 215 220

<210> 206
 <211> 382
 <212> PRT

152

<213> Homo sapiens

<400> 206

Met	Phe	Leu	Lys	Ala	Val	Val	Leu	Ser	Leu	Ala	Leu	Val	Ala	Val	Thr
1				5					10					15	
Gly	Ala	Arg	Ala	Glu	Val	Asn	Ala	Asp	Gln	Val	Ala	Thr	Val	Met	Trp
			20					25					30		
Asp	Tyr	Phe	Ser	Gln	Leu	Gly	Ser	Asn	Ala	Lys	Lys	Ala	Val	Glu	His
		35					40					45			
Leu	Gln	Lys	Ser	Glu	Leu	Thr	Gln	Gln	Leu	Asn	Thr	Leu	Phe	Gln	Asp
	50					55					60				
Lys	Leu	Gly	Glu	Val	Asn	Thr	Tyr	Thr	Glu	Asp	Leu	Gln	Lys	Lys	Leu
65					70					75					80
Val	Pro	Phe	Ala	Thr	Glu	Leu	His	Glu	Arg	Leu	Thr	Lys	Asp	Ser	Glu
				85					90					95	
Lys	Leu	Lys	Glu	Glu	Ile	Arg	Arg	Glu	Leu	Glu	Glu	Leu	Arg	Ala	Arg
			100					105						110	
Leu	Leu	Pro	His	Ala	Thr	Glu	Val	Ser	Gln	Lys	Ile	Gly	Asp	Asn	Val
		115					120					125			
Arg	Glu	Leu	Gln	Gln	Arg	Leu	Gly	Pro	Phe	Thr	Gly	Gly	Leu	Arg	Thr
	130					135					140				
Gln	Val	Asn	Thr	Gln	Val	Gln	Gln	Leu	Gln	Arg	Gln	Leu	Lys	Pro	Tyr
145					150					155					160
Ala	Glu	Arg	Met	Glu	Ser	Val	Leu	Arg	Gln	Asn	Ile	Arg	Asn	Leu	Glu
				165					170					175	
Ala	Ser	Val	Ala	Pro	Tyr	Ala	Asp	Glu	Phe	Lys	Ala	Lys	Ile	Asp	Gln
			180				185						190		
Asn	Val	Glu	Glu	Leu	Lys	Gly	Ser	Leu	Thr	Pro	Tyr	Ala	Glu	Glu	Leu
		195					200					205			
Lys	Ala	Lys	Ile	Asp	Gln	Asn	Val	Glu	Glu	Leu	Arg	Arg	Ser	Leu	Ala
	210					215					220				
Pro	Tyr	Ala	Gln	Asp	Val	Gln	Glu	Lys	Leu	Asn	His	Gln	Leu	Glu	Gly
225					230					235					240
Leu	Ala	Phe	Gln	Met	Lys	Lys	Gln	Ala	Glu	Glu	Leu	Lys	Ala	Lys	Ile
				245					250					255	
Ser	Ala	Asn	Ala	Asp	Glu	Leu	Arg	Gln	Lys	Leu	Val	Pro	Val	Ala	Glu
			260					265					270		
Asn	Val	His	Gly	His	Leu	Lys	Gly	Asn	Thr	Glu	Gly	Leu	Gln	Lys	Ser
		275					280					285			
Leu	Leu	Glu	Leu	Arg	Ser	His	Leu	Asp	Gln	Gln	Val	Glu	Glu	Phe	Arg
	290					295					300				
Leu	Lys	Val	Glu	Pro	Tyr	Gly	Glu	Thr	Phe	Asn	Lys	Ala	Leu	Val	Gln
305					310					315					320
Gln	Val	Glu	Asp	Leu	Arg	Gln	Lys	Leu	Gly	Pro	Leu	Ala	Gly	Asp	Val
				325					330					335	

<400> 207																
Met	Phe	Leu	Lys	Ala	Val	Val	Leu	Thr	Leu	Ala	Leu	Val	Ala	Val	Ala	
1				5					10					15		
Gly	Ala	Arg	Ala	Glu	Val	Ser	Ala	Asp	Gln	Val	Ala	Thr	Val	Met	Trp	
			20					25					30			
Asp	Tyr	Phe	Ser	Gln	Leu	Ser	Asn	Asn	Ala	Lys	Glu	Ala	Val	Glu	His	
		35					40					45				
Leu	Gln	Lys	Ser	Glu	Leu	Thr	Gln	Gln	Leu	Asn	Ala	Leu	Phe	Gln	Asp	
	50					55					60					
Lys	Leu	Gly	Glu	Val	Asn	Thr	Tyr	Ala	Gly	Asp	Leu	Gln	Lys	Lys	Leu	
65					70					75					80	
Val	Pro	Phe	Ala	Thr	Glu	Leu	His	Glu	Arg	Leu	Ala	Lys	Asp	Ser	Glu	
				85					90					95		
Lys	Leu	Lys	Glu	Glu	Ile	Gly	Lys	Glu	Leu	Glu	Glu	Leu	Arg	Ala	Arg	
			100					105					110			
Leu	Leu	Pro	His	Ala	Asn	Glu	Val	Ser	Gln	Lys	Ile	Gly	Asp	Asn	Leu	
		115					120					125				
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Ser	Ala	Ser	Ala	Glu	Glu	Leu	Arg	Gln	Arg	Leu	Ala	Pro	Leu	Ala	Glu	
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190

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157

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158

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325					330					335						
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His	Ser	Leu	His	Asp	Gln	Gly	His	Ser	His	Leu	Gly	Asp	Pro			
355					360					365						

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/26013**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C07K 14/47; C12N 5/10, 5/16, 15/12, 15/63, 15/64

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350; 536/23.1, 23.5, 24.3, 24.31; 435/69.1, 71.1, 71.2, 471, 325, 252.3, 254.11, 320.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92/05256 A1 (GENETICS INSTITUTE, INC., THE WISTAR INSTITUTE) 02 April 1992 (02/04/92), see entire document, especially pages 17-21.	1-12, 14-16, 21

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
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Date of the actual completion of the international search

11 DECEMBER 2000

Date of mailing of the international search report

09 JAN 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

PREMA MERTZ

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PARALEGAL SPECIALIST
TECHNOLOGY CENTER 1600

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/26013

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-12, 14-16, 21
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The computer readable form of the sequence listing is defective. Since a proper computer readable form is required to search every one of the claims, no meaningful search could be carried out.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-12, 14-16, 21

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/26013

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

530/350; 536/23.1, 23.5, 24.3, 24.31; 435/69.1, 71.1, 71.2, 471, 325, 252.3, 254.11, 320.1

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-12, 14-16, 21, drawn to a nucleic acid of SEQ ID NO:11 encoding a protein of SEQ ID NO:82, a vector, a host cell, a method of making the protein and the protein of SEQ ID NO:82.

Group II, claim 13, drawn to an antibody that binds the protein of SEQ ID NO:82.

Group III, claim 17, drawn to a method of treating a condition comprising administering the protein of SEQ ID NO:82.

Group IV, claim 18, drawn to a method of diagnosing a pathological condition using the polynucleotide encoding a protein of SEQ ID NO:82.

Group V, claim 19, drawn to a method of diagnosing a pathological condition by determining the amount of protein of SEQ ID NO:82.

Group VI, claim 20, drawn to a method of identifying a binding partner of the protein of SEQ ID NO:82.

Group VII, claims 22-23, drawn to a method of identifying an activity in a biological assay.

Group VIII, claim 17, drawn to a method for treating a condition comprising administering the nucleic acid of SEQ ID NO:11.

The inventions listed as Groups I-VIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Pursuant to 37 C.F.R. § 1.475 (d), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto. Accordingly, the main invention (Group I) comprises the first-recited product, a nucleic acid encoding a protein of SEQ ID NO:82, a vector, a host cell, a method of making the protein of SEQ ID NO:82, and the protein of SEQ ID NO:82. Further pursuant to 37

C.F.R. § 1.475 (d), the ISA/US considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

the polynucleotides set forth in Table I encoding the polypeptides set forth in Table I, pages 226-232 of the description.